Prescribing Information

Carboplatin 10 mg/ml concentrate for solution for infusion

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: 1 ml of concentrate for solution for infusion contains 10mg of Carboplatin.

Indications: Carboplatin is indicated in adults for the treatment of advanced ovarian carcinoma of epithelial origin in first line therapy and in second line therapy, after other treatments have failed; and small cell carcinoma of the lung.

Dosage and Administration: *Posology:* The recommended dosage of Carboplatin in previously untreated adult patients with normal kidney function, i.e. creatinine clearance >60 ml/min is 400 mg/m^2 as a single short term IV dose administered by a 15 to 60 minutes infusion. Alternatively, the Calvert formula may be used to determine dosage (see SmPC). Therapy should not be repeated until four 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 haematologic 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 haematological nadirs and renal function monitored. Patients with creatinine clearance 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% for 41-59 ml/min baseline creatinine clearance with initial dosage 250mg/m^2, and 16-40 ml/min baseline creatinine clearance with initial dosage 200 mg/m^2 I.V.. Insufficient data exist on the use of carboplatin injection in patients with creatinine of 15 ml/min or less to give a recommendation for treatment. All dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance and to the acceptable level of myelosuppression. *Combination Therapy*: The optimal use of carboplatin in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted. *Elderly population*: In patients of more than 65 years of age, adjustment of the carboplatin dose to the general condition is necessary during the first and the subsequent therapeutic courses. *Paediatric population*: The safety and efficacy of carboplatin in children and adolescents have not yet been established. There is insufficient information to support a dosage recommendation in the paediatric population. *Method of administration*: Carboplatin should be used by the intravenous route only.

Contraindications: Hypersensitivity to the active substance or to any of the excipients; 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 other platinum containing compounds; dosage adjustment may allow use in the presence of mild renal impairment.

Warnings and 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, neurological checks, 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.

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. 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. *Haematological Toxicity:* Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. Peripheral blood counts should be monitored during carboplatin treatment. This will monitor toxicity and help determine the nadir and recovery of haematological parameters and assist in subsequent dosage adjustments. Median day of nadir is day 21 in patients receiving single agent carboplatin and day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal. 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 marrow recovery is evident, should be considered. This recovery usually takes 5 to 6 weeks. Transfusions may be necessary and dosage reductions recommended for subsequent treatment. 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 interrupted and dose modification or discontinuation should be considered. 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. Initial carboplatin dosages in these groups of patients should be appropriately reduced and the effects carefully monitored through frequent blood counts between courses. Myelosuppressive effects may be additive to those of concomitant chemotherapy. Combination therapy with other myelosuppressive drugs may require modification of dosage or timing of schedules in order to minimize additive effects. Anaemia is frequent and cumulative, however rarely requires a transfusion. Haemolytic anaemia with the presence of serologic drug-induced antibodies has been reported in patients treated with carboplatin. This event can be fatal. *Neoplasms benign, malignant and unspecified (incl cysts and polyps):* Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS)/ acute myeloid leukaemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments. *Haemolytic-uraemic syndrome (HUS):* HUS is a life-threatening side effect. Carboplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required. *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. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction). *Renal Toxicity:* Deterioration of renal function may occur during treatment with carboplatin. 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. *Venoocclusive liver disease:* Cases of hepatic venoocclusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases. *Tumour lysis syndrome (TLS):* TLS has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken. *Neurologic Toxicity:* Although peripheral neurologic toxicity is generally common and mild, limited to paraesthesia 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):* RPLS has 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. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI. *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. *Hearing functions:* Auditory defects have been reported during carboplatin therapy. Ototoxicity may be more pronounced in children and is more likely seen in patients previously treated with cisplatin. Audiograms should be considered. Cases of hearing loss with a delayed onset have been reported in paediatric patients. A long-term audiometric follow-up in this population is recommended. *Other:* 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. The carcinogenicity of carboplatin has not been studied, but carcinogenic properties of compounds with similar mechanisms and mutagenicity have been reported. *Effects on ability to drive and use machines*: 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.

Fertility, Pregnancy & Lactation: *Contraception in males and females:* Women of childbearing potential should be advised to avoid becoming pregnant while receiving carboplatin and to use effective contraception during treatment with carboplatin and for at least 6 months after the last dose. Men of sexually mature age treated with carboplatin are advised to use effective contraceptive measures and not to father a child during treatment and up to 3 months afterwards. *Pregnancy:* No controlled studies in pregnant women have been conducted. Carboplatin is suspected to cause serious birth defects when administered during pregnancy. Both men and women receiving carboplatin should be informed of the potential risk of adverse effects on reproduction. Carboplatin should not be used during pregnancy unless the clinical condition of the woman requires treatment with carboplatin. *Breast-feeding:* Carboplatin and its active metabolites have been identified in the breast milk of treated mothers. Due to the potential for serious adverse reactions in nursing infants, breastfeeding should be discontinued during treatment and for 1 month after the last dose or treatment should be discontinued, taking into account the importance of the drug to the mother. *Fertility:* Male and female fertility may be impacted by treatment with carboplatin. Both men and women should seek advice for fertility preservation before treatment with carboplatin. Gonadal suppression resulting in amenorrhoea or azoospermia may occur in patients receiving antineoplastic therapy and patients receiving carboplatin should be warned of this potential. 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.

Adverse Events include:
Adverse events which could be considered serious: Treatment related secondary malignancy, pneumonia, thrombocytopenia, neutropenia, leukopenia, anaemia, haemorrhage, bone marrow failure, febrile neutropenia, haemolytic-uraemic syndrome (HUS), haemolytic anaemia, hypersensitivity, anaphylactoid type reaction (including dyspnoea, tachycardia, anaphylactic shock), angioedema, neuropathy peripheral, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), encephalopathy, loss of vision, ototoxicity, cardiac failure, Kounis syndrome, embolism, hypertension, venoocclusive disease, interstitial lung disease, bronchospasm, pancreatitis, exfoliative dermatitis, injection site necrosis, blood bilirubin increased, myelosuppression, pulmonary fibrosis (manifested by tightness of the

chest and dyspnoea), sight loss, acute fulminant liver cell necrosis, severe hepatic dysfunction, renal function impairment.

Other Very Common adverse events: Vomiting, nausea, abdominal pain, 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, subclinical decrease in hearing acuity in the high frequency range (4000-8000 Hz), renal toxicity.

Other Common adverse events: Infections, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia, visual disturbance, cardiovascular disorder, respiratory disorder, diarrhoea, constipation, mucous membrane disorder, alopecia, skin disorder, musculoskeletal disorder, urogenital disorder, asthenia, blood creatinine increased, blood uric acid increased, tinnitus.

See SmPC for details of other adverse events.

Presentation and Price: 1 x 50mg/5ml vial: £20.20. 1 x 150mg/15ml vial: £60.59. 1 x 450mg/45ml vial: £181.77. 1 x 600mg/60ml vial: £232.64.

Legal Category: POM

Further information is available from: Accord-UK Ltd, Whiddon Valley, Barnstaple, Devon, EX32 8NS.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Accord-UK LTD on 01271 385257 or email medinfo@accord-healthcare.com.