הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

תאריך __ December 31, 2014 __

שם תכשיר באנגלית ומספר הרישום
CARBOPLATIN 10 mg.ml Concentrate for Solution for Infusion
042 05 25540 05

שם בעל הרישום **Salomon, Levin & Elstein Ltd. POBox 3696 Petach Tikva**

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

טקסט חדש	טקסט נוכחי	פרק בעלון
		Indication
		Contraindications
Therapy should not be repeated until four weeks after the previous carboplatin course . and/or until the neutrophil count is at least 2000 cells/mm^3 and the platelet count is at least 100.000 cells/ mm^3. Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of not tolerable side effects. Paediatric population As no sufficient experience of carboplatin use in children is available, no specific dosage recommendations can be given. ~~Paediatrics~~ ~~Sufficient usage of carboplatin in paediatrics has not occurred to allow specific dosage recommendations to be made.~~	Therapy should not be repeated until four weeks after the previous carboplatin course Paediatrics Sufficient usage of carboplatin in paediatrics has not occurred to allow specific dosage recommendations to be made.	**Posology, dosage & administration**
Diagnostic and treatment facilities should be readily available for management of therapy and possible complications. Renal and hepatic function impairment may be encountered with carboplatin. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds. 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.	Renal function impairment may be encountered with carboplatin. Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds. As for other platinum co-ordination compounds, allergic reactions to carboplatin have been reported. They may occur within minutes of administration and should be managed with appropriate supportive therapy.. Anaphylactic-like reactions may also occur as with other platinum co-ordination compounds.	**Special Warnings and Special Precautions for Use**

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. As for other platinum co-ordination compounds, allergic reactions to carboplatin have been reported. 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 they may occur within minutes of administration and should be managed with appropriate supportive therapy. 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. Anaphylactic-like reactions may also occur as with other platinum co-ordination compounds. In patients pre-treated with platinum containing medicinal products, the risk of allergic reactions, including anaphylaxis, is increased. 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.	In patients pre-treated with platinum containing medicinal products, the risk of allergic reactions, including anaphylaxis, is increased.	
Administration of nephrotoxic and/or ototoxic drugs (e.g. aminoglycosides, vancomycin, capreomycin, loop diuretics) during treatment with carboplatin may increase organ toxicity of the drugs due to carboplatin induced changes in renal clearance of these substances. Caution should be exercised when carboplatin in used concomitantly with warfarin, as cases increased INR have been reported.	Administration of nephrotoxic and/or ototoxic drugs (e.g. aminoglycosides, loop diuretics) during treatment with carboplatin may increase organ toxicity of the drugs	**Interaction with Other Medicaments and Other Forms of Interaction**
		Pregnancy and Fertility, Lactation
~~***Infections and infestations***~~ ~~*Uncommon*~~ ~~Infectious complications~~ ~~*Rare*~~	***Infections and infestations*** *Uncommon* Infectious complications *Rare*	**Adverse events**

~~Life-threatening infection~~	Life-threatening infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) *Uncommon:* Secondary malignancies (including promyelocytic leukaemia which occurred 6 years after monotherapy with carboplatin and preceding irradiation) have been reported following administration of carboplatin as a single agent or in combination therapy (causal relationship not established).	***Neoplasms benign, malignant and unspecified (incl cysts and polyps)***	
~~Treatment related secondary malignancies: *Uncommon.*~~	Treatment related secondary malignancies: Uncommon.	
Blood and lymphatic system disorders *Very common* Myelosuppression is the dose-limiting toxicity of carboplatin. At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia, with nadir platelet counts of less than 50 x 10^9/l, occurs in about a third of the patients. The nadir usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy. Leucopenia (< 2000/µl) has also occurred in approximately 20% of patients but its recovery from the day of nadir (day 14 - 28) may be slower and usually occurs within 42 days from the start of therapy . Neutropenia with granulocyte counts below 1 x 109/l occurs in approximately one fifth of patients. Haemoglobin values below 9.5 mg/100 ml have been observed in 48% of patients with normal base-line values. Anaemia occurs frequently and may be cumulative.	***Blood and lymphatic system disorders*** *Very common* Myelosuppression is the dose-limiting toxicity of carboplatin. At maximum tolerated dosages of carboplatin administered as a single agent, thrombocytopenia, with nadir platelet counts of less than 50 x 10^9/l, occurs in about a third of the patients. The nadir usually occurs between days 14 and 21, with recovery within 35 days from the start of therapy. Leucopenia (< 2000/µl) has also occurred in approximately 20% of patients but its recovery from the day of nadir (day 14 - 28) may be slower and usually occurs within 42 days from the start of therapy .	
Common Haemorrhagic complications, usually minor, have also been reported. *Uncommon*: Infectious complications have occasionally been reported.	*Common* Haemorrhagic complications,	
Rare Febrile neutropenia, haemolytic uraemic syndrome. Single cases of life-threatening infections and bleeding have occurred.	*Rare* Febrile neutropenia, haemolytic uraemic syndrome.	
Immune system disorders *Common* Allergic reactions. Allergic reactions to carboplatin have been reported in less than 2% of patients, e.g., skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus. These reactions are similar to those observed after administration of other platinum-containing	***Immune system disorders*** *Common* Allergic reactions. These reactions are similar to those observed after administration of other platinum-containing compounds , i.e. erythematous rash, fever with no other apparent cause and pruritus.	

compounds and should be managed with appropriate supportive therapy. ~~, i.e. erythematous rash, fever with no other apparent cause and pruritus.~~		
Rare Anaphylaxis, anaphylactic shock, angio-oedema and anaphylactoid reactions, including bronchospasm, urticaria, facial odema and facial flushing, dyspnoea, hypotension, dizziness, wheezing, and tachycardia have occurred requiring adequate treatment (epinephrine, antihistamines, corticosteroids), hypotension, bronchospasm.	*Rare* anaphylactic shock requiring adequate treatment (epinephrine, antihistamines, corticosteroids), hypotension, bronchospasm.	
Metabolism and nutrition disorders *Very common*: Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) have been reported after treatment with carboplatin but have not been reported to be severe enough to cause the appearance of clinical signs or symptoms. *Rare*: Cases of hyponatraemia have been reported. ~~*Very common*~~ ~~Hyperuricaemia is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allupurinol.~~ ~~*Rare*~~ ~~Anorexia.~~	***Metabolism and nutrition disorders*** *Very common* Hyperuricaemia is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allupurinol. *Rare* Anorexia.	
Nervous system disorders *Common* The incidence of peripheral neuropathies after treatment with carboplatin is 6%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in patients above the age of 65 years or patients previously treated with cisplatin. Central nervous symptoms: paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin. *Uncommon*: Central nervous symptoms have been reported, however, they seem to be frequently attributed to concomitant antiemetic therapy. ~~*Rare*~~ ~~Taste alteration.~~ ~~*Very rare*~~ ~~Cerebrovascular events (apoplexy)~~	***Nervous system disorders*** *Common* The incidence of peripheral neuropathies after treatment with carboplatin is 6%. In the majority of the patients neurotoxicity is limited to paraesthesia and decreased deep tendon reflexes. The frequency and intensity of this side effect increases in patients above the age of 65 years or patients previously treated with cisplatin. Central nervous symptoms: paraesthesia present before commencing carboplatin therapy, particularly if related to prior cisplatin treatment, may persist or worsen during treatment with carboplatin. *Rare* Taste alteration. *Very rare* Cerebrovascular events (apoplexy)	

Eye disorders *Rare* 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. Optic neuritis has been reported in post marketing surveillance.	***Eye disorders*** *Rare* 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 *Very common* Subclinical decrease in hearing acuity, consisting of high-frequency (4000 - 8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin.	***Ear and labyrinth disorders*** *Very common* Subclinical decrease in hearing acuity, consisting of high-frequency (4000 - 8000 Hz) hearing loss determined by audiogram, has been reported in 15% of the patients treated with carboplatin.	
Common Clinical ototoxicity. Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen. Clinically significant hearing loss has occurred in children who received carboplatin dosages higher than recommended and combined with other ototoxic drugs.	*Common* Only 1% of patients present with clinical symptoms, manifested in the majority of cases by tinnitus. In patients who have been previously treated with cisplatin and have developed hearing loss related to such treatment, the hearing impairment may persist or worsen. Clinically significant hearing loss has occurred in children who received carboplatin dosages higher than recommended and combined with other ototoxic drugs.	
Cardiac disorders *Very rare:* Cardiovascular events (cardiac failure, embolism) as well as cerebrovascular events (apoplexy) have been reported in single cases (causal relationship with carboplatin not established). Single cases of hypertension have been reported. ~~*Very rare*~~ ~~Cardiovascular events (cardiac failure, embolism).~~ ~~***Vascular disorders***~~ ~~*Rare*~~ ~~Bleeding.~~ ~~*Very rare*~~ ~~Hypertension.~~	***Cardiac disorders*** *Very rare* Cardiovascular events (cardiac failure, embolism). ***Vascular disorders*** *Rare* Bleeding. *Very rare* Hypertension.	
Respiratory, thoracic and mediastinal disorders *Very rare:* Pulmonary fibrosis 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 *Very common* Nausea without vomiting occurs in about a quarter of the patients receiving carboplatin; vomiting has been reported in half of the patients and one-third of these suffer severe emesis. Nausea and vomiting are generally delayed until 6-12 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 seems to occur more frequently in previously treated patients, particularly in patients pre-treated with cisplatin. Painful gastro-intestinal disorders, have occurred in 17% of patients. *Common* Diarrhoea and constipation have occurred in 6% and 4% of patients, respectively. *Rare* Taste alteration. Cases of anorexia have been reported. ***Hepatobiliary disorders*** *Very common*: Abnormalities of liver function tests (usually mild to moderate) have been reported with carboplatin in about one-third of the patients with normal baseline values. The alkaline phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment. ***Renal and urinary disorders*** *Very common* Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as a high volume fluid hydration or forced diuresis. Nevertheless increasing blood urea or serum creatinine levels can occur in about 15% of patients without a hydration programme or forced diuresis. *Common* Renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min may also be observed. 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	***Gastrointestinal disorders*** *Very common* Nausea without vomiting occurs in about a quarter of the patients receiving carboplatin; vomiting has been reported in half of the patients and one-third of these suffer severe emesis. Nausea and vomiting 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. Painful gastro-intestinal disorders, have occurred in 17% of patients. *Common* Diarrhoea and constipation have occurred in 6% and 4% of patients, respectively. ***Renal and urinary disorders*** *Very common* Renal toxicity is usually not dose-limiting in patients receiving carboplatin, nor does it require preventive measures such as a high volume fluid hydration or forced diuresis. Nevertheless increasing blood urea or serum creatinine levels can occur in about 15% of patients without a hydration programme or forced diuresis. *Common* Renal function impairment, as defined by a decrease in the creatinine clearance below 60 ml/min may also be observed. The incidence and severity of nephrotoxicity may increase in	

presence of moderate alteration of renal function (creatinine clearance 41 to 59 ml/min) or severe alteration (21 – 40 ml/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 ml/min. ~~Decrease in serum electrolytes (magnesium, sodium, potassium and, rarely calcium) have been reported after treatment with carboplatin but have not been reported to be severe enough to cause the appearance of clinical signs or symptoms.~~	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 moderate alteration of renal function (creatinine clearance 41 to 59 ml/min) or severe alteration (21 – 40 ml/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 ml/min. Decrease in serum electrolytes (magnesium, sodium, potassium and, rarely calcium) have been reported after treatment with carboplatin but have not been reported to be severe enough to cause the appearance of clinical signs or symptoms.	
General disorders and administration site conditions *Very common* Hyperuricaemia is observed in about one quarter of patients. Serum levels of uric acid can be decreased by allopurinol. Asthenia. *Common:* Malaise, urticaria, flu-like syndrome, erythematous rash, pruritis. *Uncommon:* Fever and chills without evidence of infection; injection site reactions such as pain, erythema, swelling, urticaria and necrosis. *Rare:* Haemolytic uraemic syndrome. ~~*Common*~~ ~~Mucositis, malaise.~~ ~~*Uncommon*~~ ~~Injection site reactions, such as pain, erythema, swelling, urticaria and necrosis. Fever and chills without evidence of infection.~~ ~~***Investigations***~~ ~~*Very common*~~ ~~Abnormalities of liver function tests (usually mild to moderate) have been reported with carboplatin in about one-third of the patients with normal~~	***General disorders and administration site conditions*** *Very common* . Asthenia. *Common* Mucositis, malaise. *Uncommon* Injection site reactions, such as pain, erythema, swelling, urticaria and necrosis. Fever and chills without evidence of infection. ***Investigations*** *Very common* Abnormalities of liver function tests (usually mild to moderate) have been reported with carboplatin in about one-third of the patients with normal baseline values. The alkaline phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment. There is a possibility of electrolytic abnormalities.	

~~baseline values. The alkaline phosphatase level is increased more frequently than SGOT, SGPT or total bilirubin. The majority of these abnormalities regress spontaneously during the course of treatment.~~ ~~There is a possibility of electrolytic abnormalities.~~ Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. 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 professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx? formType = AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).	Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.	
Paediatric population Safety and efficacy in children have not been established.		**Pharmacodynamic properties**
Symptoms of overdose Carboplatin was administered in Phase I studies at a dosage of up to 1600mg/m^2 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, erythema, and severe infection. In the majority of cases, hearing disturbances were transient and reversible. *Therapy 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. ~~Since no known antidote exists for carboplatin, every possible measure should be undertaken to avoid an overdose.~~	Since no known antidote exists for carboplatin, every possible measure should be undertaken to avoid an overdose. No overdosage occurred during clinical trials. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity. Overdosage of the medicinal product may be associated with renal failure. Symptomatic measures should be taken to sustain the patient through any period of toxicity that might occur.	**Overdose**

~~No overdosage occurred during clinical trials. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity. Overdosage of the medicinal product may be associated with renal failure. Symptomatic measures should be taken to sustain the patient through any period of toxicity that might occur.~~		
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. 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.		**Pharmacokinetic properties**
Shelf life after first opening **6.3** Immediate and single use. **After ~~reconstitution,~~ dilution** From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. When diluted as directed, carboplatin solutions should be used within 12 hours when stored at room temperature (15 - 25°C) protected from light or within 24 hours when stored at 2 - 8°C if dilution is carried out under validated aseptic conditions. ~~When reconstitution/dilution is carried out under validated aseptic conditions, and if justified, the product may be stored for a maximum period of 24 hours (at 2 – 8° C).~~ **Special precautions for storage** **6.4** Store below 25°C. Do not refrigerate. Keep in the original package in order to protect from light. Dilution: The product may be diluted with 5% Glucose for Injection, or 0.9% Sodium Chloride for Injection, to concentrations as low as 0.5 mg/ml (500 micrograms/ml). From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.	**Shelf life after first opening** **6.3** Immediate and single use. **After reconstitution, dilution** When reconstitution/dilution is carried out under validated aseptic conditions, and if justified, the product may be stored for a maximum period of 24 hours (at 2 – 8° C). **Special precautions for storage** **6.4** Store below 25°C. Do not refrigerate. Keep in the original package in order to protect from light. Dilution: The product may be diluted with 5% Glucose for Injection, or 0.9% Sodium Chloride for Injection, to concentrations as low as 0.5 mg/ml (500 micrograms/ml). When diluted as directed, carboplatin solutions should be used within three hours when stored at room temperature (15 - 25°C) protected from light or within 24 hours when stored at 2 - 8°C if dilution is carried out under validated aseptic conditions.	**Pharmaceutical particulars**

When diluted as directed, carboplatin solutions should be used within 12 ~~three~~ hours when stored at room temperature (15 - 25°C) protected from light or within 24 hours when stored at 2 - 8°C if dilution is carried out under validated aseptic conditions. Since no antibacterial preservatives are contained in the formulation, it is recommended that any carboplatin solution be discarded 12 ~~three~~ hours after dilution if stored at room temperature protected from light or after 24 hours, if stored under refrigeration. This product is for single dose use only.	Since no antibacterial preservatives are contained in the formulation, it is recommended that any carboplatin solution be discarded three hours after dilution if stored at room temperature protected from light or after 24 hours, if stored under refrigeration. This product is for single dose use only.	