PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

CARBOPLATIN 50 mg/5 mL FRESENIUS

CARBOPLATIN 150 mg/15 mL FRESENIUS

CARBOPLATIN 450 mg/45 mL FRESENIUS

CARBOPLATIN 600 mg/60 mL FRESENIUS

Pharmaceutical form

Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate for solution for infusion contains 10 mg of carboplatin.

CARBOPLATIN 50 mg/5 mL FRESENIUS: Each 5 mL vial contains 50 mg carboplatin

CARBOPLATIN 150 mg/15 mL FRESENIUS: Each 15 mL vial contains 150 mg carboplatin

CARBOPLATIN 450 mg/45 mL FRESENIUS: Each 45 mL vial contains 450 mg carboplatin

CARBOPLATIN 600 mg/60 mL FRESENIUS: Each 60 mL vial contains 600 mg carboplatin

Sugar Free

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

A clear, colourless solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CARBOPLATIN FRESENIUS is indicated for the treatment of:

1. Advanced ovarian carcinoma of epithelial origin in:

    a) First line therapy

    b) Second line therapy, after other treatments have failed

2. Limited evidence in support of the following:

    a) Small cell carcinoma of the lung

    b) The treatment of squamous cell carcinoma of the head and neck

4.2 Posology and method of administration

Posology

The recommended dosage of CARBOPLATIN FRESENIUS in previously untreated adult patients with normal kidney function is 400 mg/m^2 as a single IV dose administered by a short term (15 to 60 minutes) infusion.

Therapy should not be repeated until four weeks after the previous Carboplatin Fresenius 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.

Reduction of the initial dosage by 20 to 25 % is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG- Zubrod 2 – 4 or Kamofsky below 80). For patients aged 65 and over, dosage adjustments, initially or subsequently, may be necessary, depending on the physical condition of the patient.

Determination of the haematological nadir by weekly blood counts during the initial courses of treatment with CARBOPLATIN FRESENIUS is recommended for future dosage adjustment.

Special populations

Impaired Renal Function:

The optimal use of CARBOPLATIN FRESENIUS in patients presenting with impaired renal function requires adequate dosage adjustment and frequent monitoring of both haematological nadirs and renal function.

Patients with creatinine clearance values below 60 mL /min are at increased risk of severe myelosuppression. The frequency of severe leucopenia, neutropenia, or thrombocytopenia has been maintained at about 25 % with the following dosage recommendations:
CARBOPLATIN FRESENIUS 250 mg/m^2 IV on day 1 in patients with baseline creatinine clearance values between 41 – 59 mL /min. CARBOPLATIN FRESENIUS 200 mg/m^2 IV on day 1 in patients with baseline creatinine clearance values between 16 – 40 mL /min.
Insufficient data exist on the use of CARBOPLATIN FRESENIUS in patients with creatinine clearance of 15 mL /min or less to permit a recommendation for creatinine clearance of 15 mL /min or less to permit a recommendation for treatment.
All of the above 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 FRESENIUS in combination with other myelosuppressive medicine requires dosage adjustments according to the regimen and schedule to be adopted.

Elderly:

Dosage adjustment, initially or subsequently, may be necessary dependent on the physical condition of the patient.

Paediatric population

Safety and efficacy in paediatrics have not been established.

Method of Administration

CARBOPLATIN FRESENIUS should be used by the intravenous route only.

4.3 Contraindications

CARBOPLATIN FRESENIUS is contraindicated in:

- hypersensitivity to the active substance or to any of the excipients listed in 6.1.
- patients with a history of severe hypersensitivity reactions to CARBOPLATIN FRESENIUS or other platinum- containing compounds.
- patients with severe pre-existing renal impairment (creatinine clearance at or below 20 **mL** /min).
- severely myelosuppressed patients and/or in patients with localized tumoral bleeding.
- concomitant use with yellow fever vaccine (see section 4.5)
- Pregnancy and lactation. (See Section 4.6)

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

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 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. Initial carboplatin dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses.

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.

Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patients with severe and persistent myelosuppression are at high risk of infectious complications including fatal outcomes (see section 4.8). If any of these events occurs, carboplatin should be discontinued.

Hypersensitivity Reactions

As with other platinum-based medicines, allergic reactions appearing most often during administration may occur and necessitate discontinuation of the 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 (see section 4.3 and section 4.8).

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8). Kounis syndrome can develop in patients with and without cardiac risk factors, and may be presented with a combination of cardiac and allergic symptoms, or as standalone. Coronary vasospasm may be eliminated with steroids, antihistamines in addition to spasmolytics treatment.

Renal Toxicity

In patients with impaired renal function, the effect of Carboplatin Fresenius on the haematopoietic system is more pronounced and longer-acting than in patients with normal renal function.
In this risk group, therapy with CARBOPLATIN FRESENIUS must be performed with special caution (see section 4.2).

Precautions:
CARBOPLATIN FRESENIUS should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic medicines. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

Peripheral blood counts, 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 medicine should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Haematological Toxicity:
Myelosuppression (leucopenia, neutropenia and thrombocytopenia) is dose- dependent and dose limiting. Peripheral blood counts should be monitored frequently and until recovery is achieved. Median day of nadir is day 21 in patients receiving single agent CARBOPLATIN FRESENIUS and day 15 in patients receiving CARBOPLATIN FRESENIUS in combination with other chemotherapeutic agents. Single intermittent courses of CARBOPLATIN FRESENIUS should not be repeated until leucocyte, neutrophil and platelet counts have returned to normal.
Transfusional support is frequently needed during treatment with CARBOPLATIN FRESENIUS, particularly in patients receiving prolonged therapy, since anaemia is

cumulative.

Myelosuppression is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial CARBOPLATIN FRESENIUS dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses.

CARBOPLATIN FRESENIUS combination therapy with other myelosuppressive forms of treatment must be planned very carefully with respect to dosages and timing in order to minimise additive effects.

Haemolytic anaemia, with the presence of serologic drug-induced antibodies, has been reported in patients treated with carboplatin. This event can be fatal.
Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS) / acute myeloid leukaemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.

Haemolytic-uremic syndrome (HUS)

Haemolytic-uremic syndrome (HUS) is a life-threatening side effect. CARBOPLATIN FRESENIUS 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.

Renal Toxicity

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.

Neurologic Toxicity

Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decrease of 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 injection 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):

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) have 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 (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

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.

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)

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patients 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.

Carboplatin dosing

Some subgroups of patients (i.e. age 40-59, BMI 20-25) are at particular risk of undertreatment if GFR is estimated using Cockroft Gault Formula. Being an accurate estimation of GFR crucial for treatment with curative intent, in such cases GFR determination using a measured standard method (inulin, 51Cr-EDTA, 99mTc-DTPA, 125I-iothalamate or iohexol) should be preferred when feasible.

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. 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. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g., aminoglycosides) (see Section 4.5).

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines including Carboplatin Fresenius, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving CARBOPLATIN FRESENIUS**.** 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 FRESENIUS (see sections 4.5 and 6.2).

Paediatric population

Not recommended in paediatric patient.

4.5 Interaction with other medicines 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 medicine.

Due to the increase of thrombotic risk in cases of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulabilty during diseases, and the possibility of interaction between oral anticoagulants and anticancer chemotherapy, may require an increase in frequency of INR monitoring if a patient is treated with oral anticoagulants.

Concomitant use contraindicated:

- Yellow fever vaccine: risk of generalised vaccinal disease mortality

Concomitant use not recommended:

- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease.

This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exist (poliomyelitis).

- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by the cytotoxic medicine or risk of toxicity enhancement or lose of efficacy of the cytotoxic medicine due to increased hepatic metabolism by phenytoin.

Concomitant use to be taken into consideration:

- Cyclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
- Concurrent therapy with nephrotoxic or ototoxic medicines such as aminoglycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.
- Loop diuretics: The concomitant use of Carboplatin Fresenius with loop diuretics should be taken into account due to the cumulative nephrotoxicity and ototoxicity.
- Combination therapy with other myelosuppressive medicines may require dose changes or rescheduling of doses in order to minimise the additive myelosuppressive effects.

Nausea and vomiting may be more severe in patients previously treated with Cisplatin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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 six months after the last dose.

Men with female partners of childbearing potential should be advised to use effective contraception during treatment with carboplatin and for at least six months after the last dose.

Pregnancy

CARBOPLATIN FRESENIUS can cause foetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats receiving the medicine during organogenesis.
Carboplatin should not be used in pregnant women or women of childbearing potential who might become pregnant (Contraindicated in pregnancy)

Breastfeeding

It is not known whether CARBOPLATIN FRESENIUS injection is excreted in human milk. To avoid possible harmful effects in the infant, breastfeeding must be stopped during carboplatin therapy.

Fertility

Male and female fertility may be impacted by treatment with carboplatin (see section 5.3). Both men and women should seek advice for fertility preservation before treatment with carboplatin.
Gonadal suppression resulting in amenorrhea or azoospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual medicines.

Men of sexually mature age treated with CARBOPLATIN FRESENIUS are advised not to father a child during treatment and up to 6 months afterwards. Men patients should seek advice about spermatic preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with CARBOPLATIN FRESENIUS.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, CARBOPLATIN FRESENIUS may cause nausea, vomiting, vision abnormalities and ototoxicity; therefore, patients must be warned on the potential effect of these events on the ability to drive or to use machines.

4.8 Undesirable effects

The frequency of adverse reactions reported is based on a cumulative database of 1,893 patients receiving single medicine carboplatin injection and post-marketing experience.
The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories:
Frequent (≥1/100)
Less frequent <1/10,000 to ≤1/100)
Not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**MedDRA Term**
Neoplasms, benign, malignant and unspecified (incl cysts and polyps)	Not known	Treatment related secondary malignancy
Infections and infestations	Frequent	Infections*
	Not known	Pneumonia
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, neutropenia, leukopenia, anaemia, haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, haemolytic-uraemic syndrome, syndrome, haemolytic anaemia (sometimes fatal)
Immune system disorders	Frequent	Hypersensitivity, anaphylactoid type reaction

Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatraemia, Tumour lysis syndrome
Nervous system disorders	Frequent	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Not known	Cerebrovascular accident*, encephalopathy, Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Eye disorders	Frequent	Visual disturbance (incl. rare cases of loss of vision)
Ear and labyrinth disorders	Frequent	Ototoxicity
Cardiac disorders	Frequent	Cardiovascular disorder*
	Not known	Cardiac failure*, Kounis syndrome
Vascular disorders	Not known	Embolism*, hypertension, hypotension, venoocclusive disease (fatal)
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory disorder, Interstitial lung disease, bronchospasm
Gastrointestinal disorders	Frequent	Vomiting, nausea, abdominal pain, diarrhoea, constipation, mucous membrane disorder
	Not known	Stomatitis, pancreatitis
Skin and subcutaneous tissue disorders	Frequent	Alopecia, skin disorder
	Not known	Urticaria, rash, erythema, pruritus
Musculoskeletal and	Frequent	Musculoskeletal disorder

connective tissue disorders		
Renal and urinary disorders	Frequent	Urogenital disorder
General disorders and administration site conditions	Frequent	Asthenia
	Not known	Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise
Investigations	Frequent	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, blood bilirubin increased, blood creatinine increased, blood uric acid increased

* Fatal in <1%, fatal cardiovascular events in <1% included cardiac failure, embolism, and cerebrovascular accident combined.

Blood and lymphatic system disorder:

Myelosuppression is the dose-limiting toxicity of Carboplatin Fresenius injection. In patients with normal baseline values, thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25 % of patients, neutropenia with granulocyte counts below 1,000/mm^3 in 18 % of patients, and leukopenia with WBC counts below 2,000/mm^3 in 14 % of patients. The nadir usually occurs on day 21.

Myelosuppression can be worsened by combination of CARBOPLATIN FRESENIUS injection with other myelosuppressive compounds or forms of treatment.

Myelotoxicity is more severe in previously treated patients, in particular in patients previously treated with cisplatin and in patients with impaired kidney function. Patients with poor performance status have also experienced increased leukopenia and thrombocytopenia. These effects, although usually reversible, have resulted in infectious and hemorrhagic complications in 4 % and 5 % of patients given carboplatin injection, respectively. These complications have led to death in less than 1% of patients.

Anaemia with haemoglobin values below 8 g/dl has been observed in 15 % of patients with normal baseline values. The incidence of anaemia is increased with increasing exposure to CARBOPLATIN FRESENIUS injection.

Neoplasms benign, malignant and unspecified (including cysts and polyps) Secondary acute malignancies after cytostatic combination therapies containing carboplatin have 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

Vomiting occurs in 65 % of patients, in one-third of whom it is severe. Nausea occurs in an additional 15 %. Previously treated patients (in particular patients previously treated with cisplatin) appear to be more prone to vomiting. Nausea and vomiting are generally delayed until 6 to 12 hours after administration of CARBOPLATIN FRESENIUS**,** are readily controlled

or prevented with antiemetics and disappear within 24 hours. Vomiting is more likely when CARBOPLATIN FRESENIUS injection is given in combination with other emetogenic compounds.

The other gastro-intestinal complaints corresponded to pain in 8 % of patients, diarrhoea, and constipation in 6 % of patients. Cramps have also been reported.

Nervous system disorders:

Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4 % of patients administered carboplatin injection.

Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with Carboplatin injection, appear to be at increased risk.

Clinically significant sensory disturbances (i.e., visual disturbances and taste modifications) have occurred in 1 % of patients.

The overall frequency of neurologic side effects seems to be increased in patients receiving CARBOPLATIN FRESENIUS injection in combination. This may also be related to longer cumulative exposure. Parasthesias present prior to treatment, especially if caused by cisplatin, may persist or worsen during carboplatin therapy (see section 4.4).

Eye disorders:

Visual disturbances, including sight loss, are 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. Very rare cases of hypoacusia have

been reported.

Tinnitus was also commonly reported. Hearing loss as a result of cisplatin therapy may give rise to persistent or worsening symptoms. Not indicated for use in paediatric patients.

Hepatobiliary disorders

Modification of liver function in patients with normal baseline values was observed, including elevation of total bilirubin in 5 %, SGOT in 15 %, and alkaline phosphatase in 24 % of patients. These modifications were generally mild and reversible in about one-half the patients.

In a limited series of patients receiving very high dosages of carboplatin injection and autologous bone marrow transplantation, severe elevation of liver function tests has occurred.

Cases of an acute, fulminant liver cell necrosis occurred after high- dosed administration of carboplatin.

Renal and urinary disorders

When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that carboplatin injection has been administered without high-volume fluid hydration and/or forced diuresis. Elevation of serum creatinine occurs in 6 % of patients, elevation of blood urea nitrogen in 14 %, and of uric acid in 5 % of patients. These are usually mild and are reversible in about one-half the patients. Creatinine clearance has proven to be the most sensitive renal function measure in patients receiving carboplatin injection. Twenty-seven percent (27 %) of patients who have a baseline value of 60 mL/min or greater, experience a reduction in creatinine clearance during carboplatin injection therapy. Impairment of renal function is more likely in patients who have previously

experienced nephrotoxicity as a result of cisplatin therapy.

Immune system disorders

Anaphylactic-type reactions, sometimes fatal, may occur most often in the minutes following injection of the product: facial oedema, dyspnoea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm.

Fever with no apparent cause has also been reported.

Skin and subcutaneous tissue disorders:

Erythematous rash, fever and pruritis have been observed. These were reactions similar to those seen after cisplatin therapy but in a few cases no cross-reactivity was present.

Investigations

Decreases in serum sodium, potassium, calcium, and magnesium occur in 29 %, 20 %, 22 %, and 29 % of patients, respectively. In particular, cases of early hyponatraemia have been reported. The electrolyte losses are minor and mostly take a course without any clinical symptoms.

Cardiac disorders

Isolated cases of cardiovascular incidents (cardiac insufficiency, embolism) as well as isolated cases of cerebrovascular accidents have been reported.

General disorders and administration site conditions:

Reactions at the site of injection (burning, pain, reddening, swelling, urticaria, necrosis in connection with extravasation) have been reported. Fever, chills and mucositis have occasionally been observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers should also report adverse reactions to the Holder of Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Treatment of overdose

There is no known antidote for carboplatin overdosage.

If necessary, the patient may need supportive treatment relating to myelosuppression, renal, hepatic and auditory function impairment. (see section 4.4). Use of higher than recommended doses of carboplatin has been associated with loss of vision.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 26 Cytostatic Agent Pharmacotherapeutic group: Antineoplastic agents, platinum compounds, ATC code: LO1XA02

Carboplatin [cis-diammine (1,1-cyclobutane-dicarboxylato) platinum] is a platinum co-ordination compound with anti-tumour properties. It is soluble in water at concentrations below 15 mg/mL.

Carboplatin, like Cisplatin, interferes with DNA intra-strand and inter-strand crosslinks in cells

exposed to the medicine. DNA reactivity has been correlated with cytotoxicity.

Paediatric population.

Safety and efficacy in children have not been established.

5.2 Pharmacokinetic properties

In patients with creatinine clearances of 60 mL/min or greater given carboplatin at doses of 300 to 500 mg/m^2, the plasma concentrations of carboplatin decay in a biphasic manner with mean alpha and beta half- lives of 1,6 hours and 3,0 hours, respectively. The total body clearance, apparent volume of distribution, and mean residence time for carboplatin are 73 mL/min, 16 L, and 3,5 hours, respectively. Carboplatin exhibits linear, dose-independent pharmacokinetics in patients with creatinine clearances > 60 mL/min. The major route of elimination of carboplatin is renal excretion.

Patients with creatinine clearances of about 60 mL/min or greater, excrete 70 % of the dose of carboplatin in the urine, with most of this occurring within 12 to 16 hours. In patients with creatinine clearances of less than 60 mL/min, carboplatin renal and total body clearances decrease progressively. Doses of carboplatin, therefore, should be reduced in patients with creatinine clearance < 60 mL/min (see section 4.2).

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

Water for Injection

6.2 Incompatibilities

Aluminium-containing equipment should not be used (see section 4.5).

6.3 Shelf life

Unopened: 2 Years

After dilution

Chemical and physical in-use stability has been demonstrated after dilution in Glucose 5 % for 96 hours at 2 ºC to 8 ºC and 20 ºC to 25 ºC. Chemical and physical in-use stability has been demonstrated after dilution in Sodium Chloride 0,9 % for 24 hours at 2 ºC to 8 ºC and 8 hours 20 ºC to 25 ºC.

6.4 Special precautions for storage

Unopened vials: Store at or below 25 °C.

Keep vial in the outer carton in order to protect from light.

After dilution: For storage conditions of the diluted medicine, see section 6.3.

6.5 Nature and contents of container

CARBOPLATIN 50 mg/5 mL FRESENIUS: Type I, clear, colorless tubular glass vial with a Chlorobutyl, flurotec coated or Bromobutyl, Omniflex Plus coated grey rubber closure with an aluminium flip–off overseal with green flip.

CARBOPLATIN 150 mg/15 mL FRESENIUS: Type I, clear, colourless tubular glass vial with a Chlorobutyl, flurotec coated or Bromobutyl, Omniflex Plus coated grey rubber closure with an aluminium flip–off overseal with blue flip.

CARBOPLATIN 450 mg/45 mL FRESENIUS: Type I, clear, colourless tubular glass vial with a Chlorobutyl, flurotec coated or Bromobutyl, Omniflex Plus coated grey rubber closure with an aluminium flip–off overseal with red flip.

CARBOPLATIN 600 mg/60 mL FRESENIUS: Type I, clear, colourless tubular glass vial with

a Chlorobutyl, flurotec coated or Bromobutyl, Omniflex Plus coated grey rubber closure with an aluminium flip–off overseal with yellow flip.
Each vial may be shrink wrapped and unit packed, with/without plastic container in carton and a leaflet is included.

6.6 Special precautions for disposal and other handling

Parenteral medicines should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particular matter is observed, shake and re-inspect. Vials with visible particulate matter should not be used.

Handling:

CARBOPLATIN FRESENIUS should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic medicines.

Contamination:

In the event of contact of CARBOPLATIN FRESENIUS 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. 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. Any unused medicine or waste material should be disposed of in accordance with local requirements.

Preparation of IV Solution:

Note warning regarding interaction of CARBOPLATIN FRESENIUS with aluminium. (See section 4.4) Carboplatin Fresenius solution may be further diluted with sufficient volumes of dextrose 5 % in water or 0,9 % sodium chloride, to concentrations as low as 0,5 mg/mL. (see section 6.3)

Note: Single dose vials, discard any unused portions. The infusion bags must be covered with aluminium foil to protect the solution from light.

7 HOLDER OF CERTIFICATE OF REGISTRATION

FRESENIUS KABI SOUTH AFRICA (PTY) LTD

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway house, Extension 7

Midrand,1685

Gauteng, South Africa

Telephone number: +27 (0)11 545 0000

8 REGISTRATION NUMBER(S)

CARBOPLATIN 50 mg/5 mL FRESENIUS: 48/26/0254

CARBOPLATIN 150 mg/15 mL FRESENIUS: 48/26/0255

CARBOPLATIN 450 mg/45 mL FRESENIUS: 48/26/0256

CARBOPLATIN 600 mg/60 mL FRESENIUS: 48/26/0257

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 December 2020

10 DATE OF REVISION OF THE TEXT