AMENDED PROPOSED PROFESSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

Accord-Carboplatin 10 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 1 ml contains: 10 mg carboplatin

3. PHARMACEUTICAL FORM

Clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Accord-Carboplatin 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 Accord-Carboplatin 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 Accord-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/mm3. Reduction of the

initial dosage by 20 - 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 Karnofsky below 80).

For patients aged 65 and over, dosage adjustment, 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 Accord-Carboplatin is recommended for future dosage adjustment.

Combination Therapy:

The optimal use of Accord-Carboplatin in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted.

Special populations

Impaired Renal Function:

The optimal use of Accord-Carboplatin 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:

Accord-Carboplatin 250 mg/m^2 IV on day 1 in patients with baseline creatinine clearance values between 41 - 59 ml/min.

Accord-Carboplatin 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 Accord-Carboplatin in patients with 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.

Paediatrics population:

Safety and efficacy in paediatrics have not been established.

Elderly:

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

Method of administration

Accord-Carboplatin should be used by the intravenous route only.

Single dose vials, discard any unused portions.

For instructions on dilution of the medicine before administration, see Section 6.6.

4.3 CONTRA-INDICATIONS:

- Accord-Carboplatin is contra-indicated in patients with a history of severe hypersensitivity reactions to carboplatin, any of the ingredients of Accord-Carboplatin or other platinum-containing compounds (see section 6.1).
- Accord-Carboplatin should not be used in patients with severe pre-existing renal impairment (creatinine clearance at or below 20 ml/min).
- Accord-Carboplatin should not be employed in severely myelosuppressed patients and/or in patients with localised tumoral bleeding.
- Pregnancy and lactation (see section 4.6).
- Concomitant use with yellow fever vaccine (see section 4.5).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Hypersensitivity reactions to Accord-Carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy (including antihistamines, adrenaline and/or glucocorticoids). There is an increased risk of allergic reactions, including anaphylaxis in patients previously exposed to platinum therapy (see sections 4.3 and 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.

Accord-Carboplatin should be used only by a medical practitioner experienced with cancer chemotherapeutic medicines. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available. Blood counts as well as renal and hepatic function tests must be done regularly and the medicines should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Myelosuppression

Myelosuppression as a result of carboplatin treatment is closely related to the renal clearance of the medicine. Therefore, in patients with abnormal renal function, or who are receiving concomitant therapy with nephrotoxic medicines, 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 carboplatin 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 medicines 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.

Renal toxicity

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

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.

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. 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~~ medicine Accord-Carboplatin and day 15 in patients receiving Accord-Carboplatin in combination with other chemotherapeutic medicines. Single intermittent courses of Accord-Carboplatin should not be repeated until leucocyte, neutrophil and platelet counts have returned to normal. Lower levels of platelets are generally seen between days 14 and 21 of initial therapy. A greater reduction is seen in patients who previously received extensive myelosuppressive chemotherapy. Lowest levels of white cells occur generally between days 14 and 28 of initial therapy. If 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 barrow recovery is evident, should be considered. This recovery usually takes 5 to 6 weeks. Transfusional support is frequently needed during treatment with Accord-Carboplatin, 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 Accord-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. Accord-Carboplatin 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 should be discontinued at the first signs of any evidence of micro-angiopathic 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.

Neurologic Toxicity:

Although peripheral neurologic toxicity is generally ~~rare~~ common and mild, limited to paraesthesia and decreases in osteotendinous reflexes, its incidence is increased in patients older than 65 years and/or in patients previously treated with platinum components, like cisplatin. Visual disturbances, including loss of vision, have been reported less frequently after the use of Accord-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. Monitoring and neurological examinations should be carried out at regular intervals.

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.

Veno-occlusive liver disease

Cases of hepatic veno-occlusive 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 medicines. Patients at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic medicines, should be monitored closely and appropriate precautions 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.

Other:

Very high dosages of Accord-Carboplatin (up to five times the single ~~agent~~ medicine recommended dose or more) have resulted in severe abnormalities in hepatic and renal function. Accord-Carboplatin carcinogenic potential has not been studied, but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

Hearing functions

Auditory defects have been reported during carboplatin therapy. Ototoxicity is more likely seen in patients previously treated with cisplatin. 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 medicines (e.g., aminoglycosides) (see Section 4.5)

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicines 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.

Note: Accord-Carboplatin interacts with aluminium to form a black precipitate and/or loss of potency. It is important not to use IV sets, needles, catheters or syringes containing aluminium parts while mixing or administering Accord-Carboplatin.

Paediatric population

Safety and effectiveness in paediatric patients have not been systematically studied.

4.5 INTERACTIONS 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 coagulability 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 disease mortal (see section 4.3).

Concomitant use not recommended

The use of Accord-Carboplatin with nephrotoxic compounds is not recommended.

Although Accord-Carboplatin has limited nephrotoxic potential, concomitant treatment with nephrotoxic or ototoxic medicines such as aminoglycosides, vancomycin, capreomycin and diuretics has resulted in episodes of increased renal and audiologic toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal

clearance. Hearing loss has been reported to occur in paediatric patients when Accord-Carboplatin was administered in combination with other ototoxic medicines. Accord-Carboplatin can induce nausea and vomiting, which can be more severe in previously treated patients (in particular in patients previously pre-treated with cisplatin).

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 exists (poliomyelitis).

Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic medicine which lead to a decrease in phenytoin serum levels); risk of toxicity enhancement or loss of efficacy of the cytotoxic medicine (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration

Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymph proliferation.

Loop diuretics: The concomitant use of carboplatin with loop diuretics should be approached with caution 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.

4.6 FERTILITY, PREGNANCY AND LACTATION:

Women of childbearing potential

It is recommended that patients with child-bearing or conceiving potential, who are receiving Accord-Carboplatin, exercise adequate contraception control.

Pregnancy

Pregnancy is a contraindication. Accord-Carboplatin has been shown to be an embryotoxin and mutagen.

Breastfeeding

Safety in lactation has not been established. It is not known whether this medicine is excreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Frequent	Infections
	Frequency unknown	Pneumonia
Neoplasms benign and malignant and unspecified (including cysts and polyps)	Frequency unknown	Treatment related secondary malignancy
Blood and the lymphatic system disorders	Frequent	Thrombocytopenia, neutropenia, leucopenia, anaemia, haemorrhage
	Frequency unknown	Myelosuppression, bone marrow failure, febrile neutropenia, haemolytic-uraemic syndrome, haemolytic anaemia (sometimes fatal)
Immune system disorders	Frequent	Hypersensitivity, anaphylactoid type reactions (including rash, urticaria, erythema, pruritus, bronchospasm, hypotension and facial oedema), anaphylaxis, angioedema
Metabolism and nutrition disorders	Frequency unknown	Dehydration, anorexia, hyponatraemia, Tumour lysis syndrome

Nervous system disorders	Frequent	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Frequency unknown	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
	Frequency unknown	Cardiac failure, Kounis syndrome
Vascular disorders	Frequency unknown	Embolism, hypertension, Hypotension, veno-occlusive 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
	Frequency unknown	Stomatitis, pancreatitis
Skin and subcutaneous tissue disorders	Frequent	Alopecia, skin disorder
	Frequency unknown	Urticaria, rash, erythema, pruritus
Musculoskeletal, connective tissue and bone disorders	Frequent	Musculoskeletal disorder
Renal and urinary disorders	Frequent	Urogenital disorder
General disorders and	Frequent	Asthenia

administration site conditions	Frequency unknown	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, elevation of blood urea, blood uric acid increased

Description of selected adverse reactions

Blood and lymphatic system disorders

Myelosuppression is the dose-limiting toxicity of carboplatin 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 1000/mm^3 in 18 % of patients, and leukopenia with WBC counts below 2000/mm^3 in 14 % of patients. The nadir usually occurs on day 21. Myelosuppression can be worsened by combination of carboplatin 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 haemorrhagic 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 injection.

Haemolytic-uremic syndrome has been reported less frequently.

Neoplasms, benign, malignant and unspecified (including cysts and polyps)

Second malignancies have been reported in association with multi-drug therapy; however the relationship to Accord-Carboplatin is unclear.

The carcinogenic potential of Accord-Carboplatin has not been studied, but compounds with a similar mechanism of action and mutagenicity have been reported to be carcinogenic. Accord-Carboplatin has been shown to be mutagenic both in vitro and in vivo. Accord-Carboplatin can cause foetal harm when administered to a pregnant woman (see Section 4.6).

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, are readily controlled or prevented with antiemetics and disappear within 24 hours. Vomiting is more likely when carboplatin injection is given in combination with other emetogenic compounds.

The other gastrointestinal 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 injection in combination. This may also be related to longer cumulative exposure. Paresthesias 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.

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-dose 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. 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 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.

Although death occurred because of cardiovascular events (cardiac failure, embolism, cerebrovascular accident) it is unclear whether this was related to chemotherapy rather than general patient conditions. Hypertension has 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.

Among miscellaneous side effects, asthenia and alopecia are the most frequent.

Malaise has also been reported.

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 professionals 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.

4.9 OVERDOSE

There is no known antidote for Accord-Carboplatin overdosage. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal function. Use of higher than recommended doses of Accord-Carboplatin has been associated with loss of vision.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Category and class: Category A: 26 – Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agent, ATC code: LO1X A02

Carboplatin [cis-diammine (1,1-cyclobutane-dicarboxylato) platinum] is a platinum co-ordination compound with antitumour properties. It is soluble in water at concentrations below 15 mg/ml. Carboplatin has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA cross links.

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 h and 3,0 h, respectively. The total body clearance, apparent volume of distribution, and mean residence time for carboplatin are 73 ml/min, 16 L, and 3,5 h, 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 h.

In patients with creatinine clearances of less than 60 ml/min, carboplatin renal and total body clearances decreases progressively. Doses of carboplatin, therefore, should be reduced in patients with creatinine clearance < 60 ml/min (see Section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Water for injection

6.2 INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

Aluminium-containing equipment should not be used.

6.3 SHELF LIFE

2 years

From a microbiological point of view, the medicine 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 8 hours at room temperature (25 °C), unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 ^{o}C. Protect from light.

For storage conditions after reconstitution and dilution of the medicine, see Section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Accord-Carboplatin 10 mg/ml Injection: 5ml, 15 ml ~~or~~ 45 ml, or 60 ml type 1 amber tubular glass vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation of IV Solution:

Accord-Carboplatin 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.

Single dose vials, discard any unused portions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 31, Ground Floor,

Woodlands Office Park,

20 Woodlands Drive, Woodmead,

Johannesburg, 2191

Tel: +27 11 234 5701/2

Email: medinfo@accordhealth.co.za

8. REGISTRATION NUMBER

41/26/0435

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/04/2008

10. DATE OF REVISION OF THE TEXT

8 July 2025