1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

SPALCARB 50 Concentrate for solution for infusion

SPALCARB 150 Concentrate for solution for infusion

SPALCARB 450 Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each 1 ml contains 10 mg carboplatin.

SPALCARB 50 contains 50 mg carboplatin (10 mg/ml)

SPALCARB 150 contains 150 mg carboplatin (10 mg/ml)

SPALCARB 450 contains 450 mg carboplatin (10 mg/ml)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SPALCARB is a clear, colourless to slightly pale yellow solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SPALCARB 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 **SPALCARB** 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 **SPALCARB** course and/or until the neutrophil count is at least 2 000 cells/mm^3 and the platelet count is at least 100 000 cells/mm^3.

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 Karnofsky 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 **SPALCARB** is recommended for future dosage adjustment.

Special populations

Impaired Renal Function:

The optimal use of **SPALCARB** 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:

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

SPALCARB 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 **SPALCARB** 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.

Combination Therapy:

The optimal use of **SPALCARB** in combination with other myelosuppressive medicines 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.

Paediatrics:

Safety and efficacy in paediatrics have not been established.

Method of administration

SPALCARB should be used by the intravenous route only.

4.3 Contraindications

SPALCARB 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 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 localised tumoral bleeding.
- concomitant use with yellow fever vaccine (see section 4.5)
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Hypersensitivity reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy.

There is an increased risk of allergic reactions, including anaphylaxis in patients previously exposed to platinum therapy (see section 4.3).

SPALCARB 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.

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 medicine **SPALCARB** and day 15 in patients receiving **SPALCARB** in combination with other chemotherapeutic medicines. Single intermittent courses of **SPALCARB** should not be repeated until leucocyte, neutrophil and platelet counts have returned to normal.

Transfusional support is frequently needed during treatment with **SPALCARB**, 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 **SPALCARB** 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. **SPALCARB** 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-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 mild, its incidence is increased in patients older than 65 years and/or in patients previously treated with platinum components.

Visual disturbances, including loss of vision, have been reported less frequently after the use of carboplatin in doses higher than those recommended in patients with renal impairment.

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. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

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.

Other:

Very high dosages of carboplatin (up to five times the single medicine recommended dose or more) have resulted in severe abnormalities in hepatic and renal function.

SPALCARB carcinogenic potential has not been studied, but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

NOTE: **SPALCARB** 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 **SPALCARB**.

Elderly 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.

Paediatric Use:

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

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 generalized disease mortal. (see section 4.3)

Concomitant use not recommended

- Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This is increased in patients who are already immunosuppressed by their underlying disease. Use 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), 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 lymphoproliferation.

- Concurrent therapy with nephrotoxic medicines or ototoxic medicines such as amino glycosides, 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 with loop diuretic 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 minimize the additive myelosuppressive effects.

Hearing loss has been reported to occur in paediatric patients when carboplatin was administered in combination with other ototoxic medicines.

SPALCARB can induce nausea and vomiting, which can be more severe in previously treated patients (in particular in patients previously pre-treated with cisplatin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

Pregnancy is a contraindication. **SPALCARB** has been shown to be an embryotoxin and mutagen (see section 4.3)

Breast-feeding

Safety in lactation has not been established. It is not known whether **SPALCARB** is excreted in breast milk (see section 4.3).

To avoid possible harmful effects in the infant, breast-feeding must be stopped during carboplatin therapy.

Fertility

Gonadal suppression resulting in amenorrhoea or azospermia 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 functional 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 **SPALCARB** are advised not to father a child during treatment and up to 6 months afterwards. Male patients should seek advice about sperm preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.

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, **SPALCARB** 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

The following adverse reactions based on frequency have been reported in patients receiving single medicine carboplatin injection.

System Organ Class	Frequency	MedDRA Term
Neoplasms, benign and malignant and unspecified (incl cysts and polyps)	Unknown	Treatment related secondary malignancy
Infections and infestations	Frequent	Infections*
	Unknown	Pneumonia
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Frequent	Haemorrhage*
	Unknown	Bone marrow failure, febrile neutropenia, haemolytic-uraemic syndrome, haemolytic anaemia
Immune system disorders	Frequent	Hypersensitivity, anaphylactoid type

		reaction
Metabolism and nutrition disorders	Unknown	Dehydration, anorexia, hyponatraemia, Tumour lysis syndrome
Nervous system disorders	Frequent	Paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia
	Less frequent	Peripheral neuropathy
	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*
	Unknown	Cardiac failure*
Vascular disorders	Unknown	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
	Unknown	Stomatitis, pancreatitis
Skin and subcutaneous tissue disorders	Frequent	Alopecia, skin disorder
	Unknown	Urticaria, rash, erythema, pruritus
Musculoskeletal and connective tissue disorders	Frequent	Musculoskeletal disorder
Renal and urinary disorders	Frequent	Urogenital disorder
General disorders and administration site conditions	Frequent	Asthenia
	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, blood uric acid increased

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

Description of selected adverse reactions:

Blood and lymphatic system disorders:

Myelosuppression is the dose-limiting toxicity of **SPALCARB** 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 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 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 patients with normal baseline values. The incidence of anaemia is increased with increasing exposure to **SPALCARB** 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, 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:

Nausea and vomiting are commonly seen. 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 **SPALCARB**, are readily controlled or prevented with antiemetics and disappear within 24 hours. Vomiting is more likely when **SPALCARB** injection is given in combination with other emetogenic compounds.

Nervous system disorders:

Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in patients administered **SPALCARB** injection. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with **SPALCARB** injection, appear to be at increased risk.

Clinically significant-sensory disturbances (ie, visual disturbances and taste modifications) have occurred in patients.

The overall frequency of neurologic side effects seems to be increased in patients receiving **SPALCARB** 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 **SPALCARB** therapy.

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 patients. 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. At higher than recommended doses, in common with other ototoxic medicines, clinically significant hearing loss has been reported to occur in paediatric patients when carboplatin is administered.

Hepatobiliary disorders:

Modification of liver function in patients with normal baseline values was observed, including elevation of total bilirubin, SGOT and alkaline phosphatase in 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 patients, elevation of blood urea nitrogen, and of uric acid in 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 **SPALCARB** injection. Patients who have a baseline value of 60 mL/min or greater, experience a reduction in creatinine clearance during **SPALCARB** 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 **SPALCARB**: 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 patients. 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.

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 **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no known antidote for **SPALCARB** 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 **SPALCARB** has been associated with loss of vision.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, Platinum compounds ATC code: LO1X A02.

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 has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal product except those mentioned in section 4.2.

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or intravenous sets containing aluminium parts that may come into contact with carboplatin should not

be used for preparation or administration of carboplatin. Precipitation can lead to a reduction of the antineoplastic activity.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light

KEEP OUT OF REACH OF CHILDREN.

After dilution

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions

6.5 Nature and contents of container

SPALCARB 50 / 150 / 450: Amber Type I glass vial with 20mm laminated chlorobutyl rubber stopper and sealed with 20 mm light blue coloured flip-off seal in unit carton

6.6 Special precautions for disposal of a used medicine

The product should be used immediately after opening.

Preparation of IV Solution:

Note warning regarding interaction of **SPALCARB** with aluminium.

SPALCARB 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.

The infusion bags must be covered with

aluminium foil to protect the solution from light.

The normal safety precautions for cytostatic medicines must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.

If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Discard after single use.

Discard any unused portion.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban. 4091

8 REGISTRATION NUMBER(S)

SPALCARB 50: 55/26/0434

SPALCARB 150: 55/26/0435

SPALCARB 450: 55/26/0436

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT