APPROVED PACKAGE INSERT

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

CISACOR 10 (Infusion solution)

CISACOR 50 (Infusion solution)

For single IV use only

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution for infusion contains 1 mg cisplatin.

Excipients with known effect: Each ml of solution for infusion contains 3,5 mg sodium.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless to pale yellow solution in amber glass vials. When examined under suitable conditions of visibility should be practically free from particles.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Cisacor is indicated for advanced, non- seminomatous testicular cancer in combination therapy with bleomycin and vinblastine; carcinoma of the ovary, particularly when used with cyclophosphamide or doxorubicin, cancers of the bladder, head and neck, endometrium, small cell carcinoma of the lung, lymphomas and some neoplasms of childhood.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Amendments have been effected according to MCC recommendations, and the package insert is free of typographical and grammatical errors.

Initials:

Cisacor is given by intravenous infusion not more frequently than every 3 to 4 weeks. It is usually given as a single dose of 50 to 120 mg per m^2 body-surface or in a dose of 15 to 20 mg per m^2 daily for 5 days. Subsequent doses should be adjusted according to the nadir of the white-blood cell and platelet counts or before renal function approaches normal. Auditory acuity must also be within normal limits. Lower doses may be required when Cisacor is given as part of a combination regimen. Lower doses may be given ranging from 20 mg per m^2 upwards every 3 to 4 weeks.

In order to prevent renal toxicity, hydration of the patient is recommended by infusion of 1 to 2 litres of suitable fluid containing 37,5 g mannitol for intravenous infusion for 8 to 12 hours before administration of Cisacor. Adequate hydration and urinary output must be maintained before and for 24 hours after administration. Concurrent furosemide may also be used provided that salt and water depletion are avoided. Any solution not used must be discarded.

Dosage adjustments are needed in cases of impaired renal function, use in elderly patients or used in combination with other myelosuppressive agents.

Method of administration

For intravenous infusion.

Note: Cisacor is incompatible with aluminium, do not use needles, intravenous sets or equipment containing aluminium for administration since an interaction may occur and a black precipitate will form.

Guidelines for handling of antineoplastic agents must be followed. Cautious and proper disposal of needles, syringes, containers and unused medication must be done.

For instructions on dilution and preparation refer to section 6.6.

4.3 CONTRA-INDICATIONS

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Initials:

- Hypersensitivity to Cisacor or any other platinum containing product, or any ingredient contained in Cisacor (listed in section 6.1).
- Cisplatin is contra-indicated in renal or hearing impairment or bone marrow depression
- Pregnancy and Lactation (see 'Pregnancy and Lactation').
- The use of live vaccines is contra-indicated in patients receiving Cisacor.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cisacor should be administered under the supervision of a qualified medical practitioner experienced in the use of antineoplastic therapy. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.
Serious toxic effects can occur on the kidneys, bone-marrow and ears. These effects are generally dose related and cumulative, and may require dosage adjustment.

Peripheral blood counts must be monitored closely. Blood counts, at the beginning of therapy and weekly, to assess the haematological nadir for dose adjustment are recommended. With leukopenia and thrombocytopenia, the leukocyte and platelet counts reach a nadir between 18 and 23 days after a dose, with recovery within 39 days. Coombs positive haemolytic anaemia has also been reported. There have been reports of acute myelogenous leukaemias and myelodysplastic syndromes arising in patients who have been treated with Cisacor, mostly when given in combination with other potentially leukemogenic agents.

Neuropathies:
Neurological evaluations should be performed prior to initiation and at periodic intervals during therapy. Treatment should be stopped if signs of peripheral neuropathies, including optic neuritis, papilloedema, cerebral blindness and seizures develop. These neuropathies may be irreversible and may manifest by paraesthesia, areflexia and a proprioceptive loss and loss of vibration perception. Loss of motor function has also been reported.

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Initials:

Neurotoxicity appears to be cumulative. Prior to each course, the absence of symptoms of peripheral neuropathy should be established.

Nephrotoxicity:

Because of cumulative nephrotoxicity, creatinine clearance and serum creatinine concentrations and blood urea should be measured prior to initiation of therapy and before each course of Cisacor to detect renal toxicity. Damage to the renal tubules may be evident during the second week after a dose of Cisacor. It is generally dose related and cumulative, but may become irreversible at high doses or with repeated administration and may be fatal. Cisplatin should not be given more frequently than once every 3-4 weeks.

Intensive hydration may ameliorate nephrotoxic effects. A urine output of 100 ml/hour or greater will tend to minimise cisplatin nephrotoxicity. This can be accomplished by

prehydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 ml/m^2/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g., mannitol).

Electrolyte disturbances, particularly hypomagnesaemia and hypocalcaemia may occur, possibly as a result of renal tubular damage. The destruction of large numbers of cells during therapy and the consequent release of breakdown products may lead to hyperuricaemia and acute renal failure due to uric acid nephropathy. High or repeated Cisacor doses can increase the severity and duration of renal impairment and may produce irreversible renal insufficiency. The concomitant use of other nephrotoxic components should be avoided.

Ototoxicity:

Since ototoxicity is cumulative and deafness may occur, an audiometric test must be performed prior to each dose. The concomitant use of other nephrotoxic or ototoxic medicines should be avoided. Ototoxicity is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). Decreased ability to hear conversational tones may occur occasionally. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however, deafness after initial dose of cisplatin has been reported rarely. Ototoxicity may be enhanced with prior simultaneous cranial irradiation and may be related to peak plasma concentration of cisplatin. It is unclear whether cisplatin induced ototoxicity is reversible.

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Initials:

Because of the possibility of carcinogenicity and mutagenicity of Cisacor, patients of child bearing age or conceiving potential must exercise non-hormonal conception control.

Severe nausea and vomiting occur in most patients 1 to 4 hours after a dose and may persist for up to a week. It may be treated or prevented by anti-emetic medication.

Allergic phenomena:

Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin and have been alleviated by administration of adrenaline, steroids and antihistamines.

As with other platinum-based products, hypersensitivity reactions appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

Hepatic function and haematological formula:

The haematological formula and hepatic function must be monitored at regular intervals.

Injection site reactions:

Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

Other:

This cytostatic medicine had a more marked toxicity than is usually found in antineoplastic chemotherapy.

Renal toxicity, which is above all cumulative, is severe and requires particular precautions during administration (see sections 4.2 and 4.8).

Close supervision must also be carried out with regard to ototoxicity, myelosuppression and anaphylactic reactions (see section 4.8).

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Initials:

As with all other potentially toxic products, precautions are essential when handling the cisplatin solution. Skin lesions are possible in the event of accidental exposure to the product. It is advisable to wear gloves. In the event the cisplatin solution comes into contact with the skin or mucous membranes, wash the skin or mucous membranes vigorously with soap and water.

Conforming to the procedures appropriate for the manipulation and elimination of cytostatic medicines is recommended (see section 6.6).

Excipients:

This medicine contains 3,5 mg sodium per ml of solution. To be taken into consideration in patients on a controlled sodium diet.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Nephrotoxic medicines: Cisacor produces cumulative nephrotoxicity that is potentiated by aminoglycoside antibiotics. Concurrent administration of Cisacor and an aminoglycoside within 1-2 weeks after Cisacor therapy has been associated with an increased risk of nephrotoxicity and acute renal failure (sometimes severe). Furosemide, ethacrynic acid, hydralazine and propanolol may increase nephrotoxicity. Concomitant use of other nephrotoxic medicines (e.g. amphotericin B) is not recommended during Cisacor therapy.

Ototoxic medicines: Patients receiving Cisacor and other potentially ototoxic medicines such as aminoglycoside antibiotics or loop diuretics (e.g. ethacrynic acid, furosemide) concomitantly, may increase the potential of Cisacor to cause ototoxicity and should be carefully monitored for signs of ototoxicity. Antihistamines, buclizine, cyclizine, loxapine, meclizine, phenothiazines, thioxanthenes or trimethobenzamide may mask the symptoms of ototoxicity.

Ifosfamide may increase hearing loss due to cisplatin.

Antineoplastic agents: Literature indicates that Cisacor may alter the renal elimination of bleomycin and methotrexate, possibly as a result of cisplatin-induced nephrotoxicity, and enhance their toxicity. The renal

toxicity of ifosfamide may be greater when used with cisplatin or in patients who have previously been given cisplatin.

Reduction of the blood's lithium values was noticed in a few cases after treatment with cisplatin combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium values.

Anticonvulsants: Patients receiving Cisacor and phenytoin, serum concentrations of the latter may be decreased, possibly as a result of decreased absorption and/or increased metabolism. In these patients, serum levels of phenytoin should be monitored and dosage adjustment made as necessary.

Serum concentrations of anticonvulsive medicines may remain at subtherapeutic levels during treatment with cisplatin.

The following medications may also interact with Cisacor and the reactions are dose dependent. Blood dyscrasia causing medications, bone marrow depressants (e.g. adriamycin) or radiotherapy and killed virus vaccines.

Anti-gout agents e.g. allopurinol, colchicine, probenecid or sulfinpyrazone can increase the risk of uric acid nephropathy.

Cisacor is rapidly degraded by bisulphite or metabisulphite and admixtures with preparations containing these as preservatives may result in loss of activity.

Mixtures with sodium bicarbonate, potassium chloride and/or etoposide may cause precipitation of Cisacor. The stability of Cisacor when mixed with fluorouracil is limited.

In the event of simultaneous use of oral anticoagulants, it is advisable to regularly check the INR.

Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33 % and therefore can intensify neurotoxicity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Cisacor is contra-indicated during pregnancy and lactation as it crosses the placenta. Cisacor may cause foetal harm when administered to a pregnant woman. Cisacor has been shown to be teratogenic, carcinogenic

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Initials:

and embryotoxic in mice and rats. Cisplatin has been reported to be found in human milk, patients receiving Cisacor should not breastfeed.

Males undergoing Cisacor therapy should use barrier contraceptive measures.

4.7 EFFECTS ON THE ABILITY TO DRIVE AND OPERATE MACHINERY

There are no known effects of Cisacor on the ability to drive or operate machinery. However, the side-effects of Cisacor may reduce the patient's driving skills and abilities to operate machinery.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Many of the adverse effects of Cisacor are an extension of their therapeutic action, which is not selective for malignant cells, but affects rapidly dividing cells. Consequently, adverse effects may be expected where normal cell division is fairly rapid, e.g. the bone marrow, lymphoreticular tissue, gastro-intestinal mucosa, skin and gonads, as well as in the foetus.

The most frequently reported adverse events of cisplatin were haematological leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricemia) and fever.

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Frequent	Sepsis
	Frequency unknown	Infection*
Neoplasms benign and malignant and unspecified (including cysts and polyps)	Less frequent	Acute leukaemia

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Initials:

Blood and the lymphatic system disorders	Frequent	Leukopenia, anaemia, thrombocytopenia is the result of dose related and reversible myelosuppression
	Frequency unknown	Coombs positive haemolytic anaemia, thrombotic microangiopathy (haemolytic uraemic syndrome)
Immune system disorders	Less frequent	Anaphylactoid reaction**
Endocrine disorders	Less frequent	Syndrome of inappropriate antidiuretic hormone (SIADH), hyperuricaemia
	Frequency unknown	Blood amylase increased
Metabolism and nutrition disorders	Frequent	Hyponatraemia
	Less frequent	Hypomagnesaemia
	Frequency unknown	Dehydration, hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalaemia, tetany
Nervous system disorders	Frequent	Peripheral neuropathies, cerebrovascular accident.
	Less frequent	Convulsion, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
	Frequency unknown	Autonomic neuropathy, slurred speech, loss of taste, memory loss. Neurological effects were reported after a single dose or prolonged therapy and may be severe and irreversible. Lhermitte's sign and autonomic neuropathy have also been reported. Central neurotoxicity includes focal encephalopathy, seizures,

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Initials:

		aphasia and cortical blindness. Haemorrhagic stroke, ageusia, cerebral arteritis.
Eye disorders	Less frequent	Optic neuritis, papilloedema and cortical blindness which are usually reversible after treatment withdrawal
	Frequency unknown	Vision blurred, colour blindness acquired, retinal pigmentation
Ear and labyrinth disorders	Less frequent	Ototoxicity: It may be more severe in children and it can manifest as tinnitus, loss of hearing in the high frequency range and occasionally deafness or vestibular toxicity.
	Frequency unknown	Tinnitus, deafness
Cardiac disorders	Frequent	Dysrhythmia, tachycardia, bradycardia
	Less frequent	Cardiovascular abnormalities e.g., coronary artery disease, congestive heart failure, postural hypotension, thrombotic angiopathy. Myocardial infarction, cardiac arrest.
Vascular disorders	Frequent	Venous thromboembolism
	Frequency unknown	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Less frequent	Pulmonary toxicity
Gastrointestinal disorders	Frequent	Nausea, vomiting
	Less frequent	Stomatitis, loss of appetite
	Frequency unknown	Gingival platinum line, anorexia, hiccups
Hepato-biliary disorders	Less frequent	Mild and transient elevations of serum AST and ALT levels
	Frequency unknown	Blood bilirubin increased

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Initials:

Skin and subcutaneous tissue disorders	Less frequent	Alopecia
	Frequency unknown	Rash
Musculoskeletal and connective tissue disorders	Less frequent	Myalgia
	Frequency unknown	Muscle spasms
Renal and urinary disorders	Frequent	Acute renal toxicity
	Frequency unknown	Renal failure acute, renal failure#, renal tubular disorder
Reproductive system and breast disorders	Less frequent	Impairment of spermatogenesis and azoospermia
General disorders and administration site conditions	Less frequent	Pyrexia. In addition, Cisacor is an irritant and can produce local pain, irritation, and inflammation at the administration site; extravasations may lead to ulceration and necrosis

*Infectious complications have led to death in some patients.

**An allergic reaction can occur within minutes of administration and includes dizziness or fainting, fast heartbeat, swelling of face and wheezing and should be treated with supportive therapy. Anaphylactic reactions can occur and supportive treatment should be available

#Elevations in BUN and creatinine, serum uric acid, and/or decrease in creatinine clearance are subsumed under renal insufficiency/failure.

4.9 OVERDOSE

See 'Side effects'

CAUTION IS ESSENTIAL IN ORDER TO PREVENT AN INADVERTANT OVERDOSE.

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Initials:

An acute overdose of cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal.

There is no specific antidote in the event of an over dosage of cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of cisplatin to proteins.

Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

A.26 Cytostatic agents

Pharmacotherapeutic group: Other antineoplastic agents, Platinum compounds, ATC code: L01XA01

Cisplatin is a platinum compound with antitumour properties.

The platinum complexes can react with DNA forming both interstrand and intrastrand DNA cross links. In addition to its reactivity with DNA, cisplatin can react with other nucleophiles, such as sulfhydryl group's proteins.

5.2 PHARMACOKINETIC PROPERTIES

There is no phase specificity in the action of cisplatin on the cell cycle. After rapid intravenous administration the medicine has an initial half-life in plasma of 25-50 minutes; concentrations decline subsequently with a half-life of 58-73 hours. More than 90 % of the platinum in the blood is bound to plasma proteins. High concentrations of cisplatin are found in the kidney, liver, intestine and testes, but there is poor penetration into the central nervous system.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection

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Initials:

6.2 INCOMPATIBILITIES

Cisacor is incompatible with aluminium, do not use needles, intravenous sets or equipment containing aluminium for administration since an interaction may occur and a black precipitate will form.

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 SHELF LIFE

36 months

After dilution with the recommended intravenous fluids, Cisacor is chemically and physically stable for 21 or 14 days at 20-25 °C at 0,01 mg/ml and 0,1 mg/ml concentration respectively. The diluted solution should be protected from light. Do not store diluted solutions in the refrigerator or freezer.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and dilution should take place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 °C. Do not refrigerate. Store in unit carton until before use. Protect from light. Any unused portion must be discarded.

KEEP OUT OF REACH OF CHILDREN.

6.5 NATURE AND CONTENTS OF CONTAINER

Cisacor 10: is packaged in a 10 ml, USP type 1 amber glass vial with a grey rubber stopper/grey Westar rubber stopper silicon 1 and a 20 mm aluminium flip-off transparent white seal, which is further packed in an outer cardboard carton.

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Initials:

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Cisacor 50: is packaged in a 50 ml, USP type 1 amber glass vial with a grey rubber stopper /grey Westar rubber stopper silicon 1 and a 20 mm aluminium flip-off transparent white seal, which is further packed in an outer cardboard carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Guidelines for handling of antineoplastic agents must be followed. Cautious and proper disposal of needles, syringes, containers and unused medication must be done.

Preparation of the intravenous administration

Take the quantity of the solution that is needed from the vial and dilute with at least 1 litre of the following solutions:

- sodium chloride 0,9 %
- mixture of sodium chloride 0,9 % / dextrose 5 % (1:1), (resulting final concentrations: sodium chloride 0,45 %, dextrose 2,5 %)
- 5 % dextrose and 0,45 % sodium chloride injection
- 5 % dextrose and 0,9 % sodium chloride with 1,875 % mannitol
- 5 % dextrose and 0,45 % sodium chloride with 1,875 % mannitol
- 5 % dextrose and 0,3 % sodium chloride with 1,875 % mannitol
- 0,45 % sodium chloride and 2,5 % dextrose

Always look at the solution before use. If the solution is not clear or an undissolved precipitate is formed the solution must not be used. Only a clear solution, free from particles should be administered.

DO NOT bring Cisacor in contact with injection material that contains aluminium.

DO NOT administer Cisacor undiluted.

Any unused product or waste should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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Initials:

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Accord Healthcare (Pty) Ltd

Tuscany Office Park, 6 Coombe Place,

Rivonia,

Gauteng, South Africa

8. REGISTRATION NUMBERS

Cisacor 10: A43/26/1019

Cisacor 50: A43/26/1021

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

Date of registration: 7 December 2012

10. DATE OF REVISION OF THE TEXT

Date of latest text as approved by Council: 05 February 2015

12/03/2021

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