PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. **NAME OF THE MEDICINE:**

CISPLATIN 50 mg/50 ml OETHMAAN (Solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 1,0 ml solution for infusion contains 1,0 mg cisplatin.

Contains approximately 180 mg (7.8 mmol) of sodium per 50 ml.

Contains sugar (Mannitol 50 mg per 50 ml).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear colourless to pale yellow solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

CISPLATIN 50 mg/50 ml OETHMAAN 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

CISPLATIN 50 mg/50 ml OETHMAAN 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 **CISPLATIN 50 mg/50 ml OETHMAAN** 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.

Special populations:

Patients with impaired renal function

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 **CISPLATIN 50 mg/50 ml OETHMAAN**. 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.

Elderly patients

Cisplatin is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

Patients taking myelosuppressive agents

If cisplatin is used in combination therapy, the dose of cisplatin must be reduced. A typical dose is 20 mg per m^2 upwards every 3 to 4 weeks.

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

CISPLATIN 50 mg/50 ml OETHMAAN is given by intravenous infusion not more frequently than every 3 to 4 weeks

Any solution not used must be discarded.

For instructions on preparation of the intravenous solution of **CISPLATIN 50 mg/50 ml OETHMAAN** before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to **CISPLATIN 50 mg/50 ml OETHMAAN** or any other platinum containing product, or any ingredient contained in **CISPLATIN 50 mg/50 ml OETHMAAN**.
- Cisplatin is contraindicated in renal or hearing impairment or bone marrow depression.
- Pregnancy and lactation (see section 4.6).
- The use of live vaccines is contraindicated in patients receiving **CISPLATIN 50 mg/50 ml OETHMAAN.**

4.4 Special warnings and precautions for use

CISPLATIN 50 mg/50 ml OETHMAAN 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 **CISPLATIN 50 mg/50 ml OETHMAAN**, mostly when given in combination with other potentially leukemogenic agents.

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.

Nephrotoxicity: Damage to the renal tubules may be evident during the second week after a dose of **CISPLATIN 50 mg/50 ml OETHMAAN**. It is generally dose related and cumulative, but may become irreversible at high doses or with repeated administration and may be fatal.
Intensive hydration may ameliorate nephrotoxic effects.

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 **CISPLATIN 50 mg/50 ml OETHMAAN** to detect renal toxicity. Urine output of 100 ml/hr or greater will tend to minimise cisplatin toxicity. 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 hyperuricemia and acute renal failure due to uric acid nephropathy. High or repeated **CISPLATIN 50 mg/50 ml OETHMAAN** 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.

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.

Because of the possibility of carcinogenicity and mutagenicity of **CISPLATIN 50 mg/50 ml OETHMAAN**, patients of child bearing age or conceiving potential must exercise non-hormonal conception control.

Severe nausea and vomiting occurs 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.

Excipient Information

CISPLATIN 50 mg/50 ml OETHMAAN contains sugar (mannitol) which may have a mild laxative effect.

CISPLATIN 50 mg/50 ml OETHMAAN contains 180 mg of sodium in each 50 ml vial, equivalent to 9,1 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Nephrotoxic medicines: CISPLATIN 50 mg/50 ml OETHMAAN produces cumulative nephrotoxicity that is potentiated by aminoglycoside antibiotics. Concurrent administration of **CISPLATIN 50 mg/50 ml OETHMAAN** and an aminoglycoside within 1-2 weeks after **CISPLATIN 50 mg/50 ml OETHMAAN** therapy has been associated with an increased risk of nephrotoxicity and acute renal failure (sometimes severe). Furosemide, ethacrynic acid, hydralazine and propranolol may increase nephrotoxicity. Concomitant use of other nephrotoxic medicines (e.g. amphotericin B) is not recommended during **CISPLATIN 50 mg/50 ml OETHMAAN** therapy.

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.

Ototoxic medicines: Patients receiving **CISPLATIN 50 mg/50 ml OETHMAAN** and other potentially ototoxic medicines such as aminoglycoside antibiotics or loop diuretics (e.g. ethacrynic acid, furosemide) concomitantly, may increase the potential of **CISPLATIN 50 mg/50 ml OETHMAAN** to cause ototoxicity and should be carefully monitored for signs of ototoxicity.

Antihistamines, Phenothiazines and others: Antihistamines, buclizine, cyclizine, loxapine, meclizine, phenothiazines, thioxanthenes or trimethobenzamide may mask the symptoms of ototoxicity (such as dizziness and tinnitus).
Ifosfamide may increase hearing loss due to cisplatin.

Antineoplastic agents: Literature indicates that **CISPLATIN 50 mg/50 ml OETHMAAN** may alter the renal elimination of bleomycin and methotrexate, possibly as a result of cisplatin-induced nephrotoxicity, and enhance their toxicity.
Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33 % and therefore can intensify neurotoxicity.

Anti-epileptics: Patients receiving **CISPLATIN 50 mg/50 ml OETHMAAN** 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.

The following medicines may also interact with **CISPLATIN 50 mg/50 ml OETHMAAN** and the reactions are dose dependent:
Blood dyscrasia causing medicines, bone marrow depressants (e.g. adriamycin) or radiotherapy and killed virus vaccines.

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

CISPLATIN 50 mg/50 ml OETHMAAN 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 **CISPLATIN 50 mg/50 ml OETHMAAN**.
The stability of **CISPLATIN 50 mg/50 ml OETHMAAN** when mixed with fluorouracil is limited.

Weakened live vaccines: Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease (see section 4.3). In view of the risk of generalised illness, it is advisable to use an inactive vaccine if available.

Oral anticoagulants:

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

Anticonvulsive substances:

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

4.6 Fertility, pregnancy and lactation

The use of **CISPLATIN 50 mg/50 ml OETHMAAN** is contraindicated during pregnancy and lactation as it crosses the placenta (see section 4.3).

Pregnancy:

CISPLATIN 50 mg/50 ml OETHMAAN may cause foetal harm when administered to a pregnant woman. **CISPLATIN 50 mg/50 ml OETHMAAN** has been shown to be teratogenic, carcinogenic and embryotoxic in mice and rats.

During treatment with CISPLATIN 50 mg/50 ml OETHMAAN and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes, e.g., Males undergoing **CISPLATIN 50 mg/50 ml OETHMAAN** therapy should use barrier contraceptive measures.

Breastfeeding:

Cisplatin has been reported to be found in human milk, patients receiving **CISPLATIN 50 mg/50 ml OETHMAAN** should not breast-feed

Fertility:

Genetic consultation is recommended if the patient wishes to have children after ending treatment.

Since a treatment with cisplatin may cause irreversible infertility, it is recommended that men, who wish to become fathers in the future, ask for advice regarding cryo-conservation of their sperm prior to treatment.

4.7 Effects on ability to drive and use machines

There are no known effects of **CISPLATIN 50 mg/50 ml OETHMAAN** on the ability to drive or operate machinery. However, the side-effects of **CISPLATIN 50 mg/50 ml OETHMAAN** like dizziness and blurred vision may reduce the patient's driving skills and abilities to operate machinery.

4.8 Undesirable effects

Many of the adverse effects of **CISPLATIN 50 mg/50 ml OETHMAAN** 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 following adverse events have been reported in association with **CISPLATIN 50 mg/50 ml OETHMAAN** therapy:

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Sepsis	Frequent
	Infection[a]	Frequency unknown
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	Acute leukaemia	Less frequent
Blood and lymphatic system disorders	Bone marrow failure, thrombocytopenia, leukopenia, anaemia is the result of dose related and reversible myelosuppression.	Frequent
	Coombs positive haemolytic anaemia, thrombotic microangiopathy (haemolytic uraemic syndrome)	Frequency unknown
Immune system disorders	Allergic reactions: 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.	Less frequent

	Anaphylactic reactions[b] can occur and supportive treatment should be available.	
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone (SIADH), hyperuricaemia.	Less frequent
	Blood amylase increased	Frequency unknown
Metabolism and nutrition disorders	Asymptomatic hypomagnesemia	Frequent
	Symptomatic hypomagnesaemia, hyponatraemia.	Less frequent
	Dehydration, hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalcaemia, tetany	Frequency unknown
Nervous system disorders	Peripheral neuropathies, cerebrovascular accident	Frequent
	Leukoencephalopathy, reversible posterior leukoencephalopathy syndrome	Less frequent
	Autonomic neuropathy, seizures, slurred speech, loss of taste, memory loss. Neurological effects were reported after a single dose or prolonged therapy and may be severe	Frequency unknown

	and irreversible. Peripheral neuropathies (e.g. paraesthesia of the upper and lower extremities), Lhermitte's sign and autonomic neuropathy have also been reported. Central neurotoxicity includes focal encephalopathy, seizures, aphasia, haemorrhagic stroke, cerebral arteritis, myelopathy	
Eye disorders:	Optic neuritis, papilloedema and cortical blindness which are usually reversible after treatment withdrawal.	Less frequent
	Blurred vision, colour blindness acquired, retinal pigmentation	Frequency unknown
Ear and labyrinth disorders	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.	Less frequent
Cardiac disorders	Tachycardia, dysrhythmia, cardiovascular abnormalities e.g. coronary artery disease, congestive heart failure, postural hypotension, thrombotic angiopathy, myocardial infarction, cardiac arrest	Less frequent

Vascular disorders	Thromboembolism leading to thromboembolic events e.g. cerebrovascular accidents.	Frequent
	Raynaud's phenomenon	Frequency unknown
Gastrointestinal disorders	Nausea and vomiting	Frequent
	Stomatitis, loss of appetite	Less frequent
	Gingival platinum line, hiccups, diarrhoea	Frequency unknown
Hepatobiliary disorders	Mild and transient elevations of serum AST and ALT levels	Less frequent
	Blood bilirubin increased	Frequency unknown
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	Frequency unknown
Skin and subcutaneous tissue disorders	Alopecia	Less frequent
	Rash	Frequency unknown
Musculoskeletal, connective tissue and bone disorders	Myalgia	Less frequent
Renal and urinary disorders	Acute renal toxicity	Frequent
	Acute renal failure, renal failure[c], renal tubular disorder	Frequency unknown

Reproductive system and breast disorders	Impairment of spermatogenesis and azoospermia	Less frequent
General disorders and administration site conditions	Pyrexia. In addition, cisplatin is an irritant and can produce local pain, irritation, and inflammation at the administration site; extravasations may lead to ulceration and necrosis.	Less frequent
	Asthenia, malaise	Frequency unknown

a: Infectious complications have led to death in some patients. b: Symptoms include facial oedema, flushing, wheezing, bronchospasm, tachycardia, and hypotension.

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

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

4.9 Overdose:

CAUTION IS ESSENTIAL IN ORDER TO PREVENT AN INADVERTANT OVERDOSE.

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 is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A26. 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.

There is no phase specificity in the action of cisplatin on the cell cycle.

5.2 Pharmacokinetic properties

Absorption

There is good uptake of cisplatin by the kidneys, liver and intestine. More than 90 % of platinum containing species remaining in the blood are bound (possibly irreversibly) to plasma proteins.

Penetration into the CSF is poor although significant amounts of cisplatin can be detected in intracerebral tumours.

Distribution

The clearance of total platinum from plasma is rapid during the first four hours after intravenous administration, but then proceeds more slowly because of covalent binding to serum proteins.

Levels of unbound platinum fall with a half-life of 20 minutes to 1 hour depending on the rate of drug infusion.

Elimination

The elimination of intact drug and various platinum-containing biotransformation products is via the urine. About 15-25 % of administered platinum is rapidly excreted in the first 2-4 hours after administration of cisplatin. This early excretion is mostly of intact cisplatin. In the first 24 hours after administration, 20-80 % is excreted, the remainder representing drug bound to tissues or plasma protein.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Mannitol pyrogen free

Hydrochloric acid

Water for injection

6.2 Incompatibilities

CISPLATIN 50 mg/50 ml OETHMAAN 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.

There is a total loss of cisplatin in 30 minutes at room temperature when mixed with metoclopramide and sodium metabisulfite in concentrations equivalent to those that would be found on mixing with a commercial formulation of metoclopramide.

Cisplatin and sodium bisulfite have been known to react chemically. Such antioxidants might inactivate cisplatin before administration if they are present in intravenous fluids.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Prior to first use: Store below 30 °C. Do not refrigerate. Protect from light. Keep vial in the outer carton until required for use. Discard any unused portion.

After dilution: After dilution with the recommended intravenous fluids, **CISPLATIN 50 mg/50 ml OETHMAAN** is chemically and physically stable for 12 hours at 20-25 ˚C. 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. Discard any unused portion.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

CISPLATIN 50 mg/50 ml OETHMAAN is packaged in a 50 ml, type 1 amber glass vial with a grey rubber stopper and a 20 mm aluminium flip-off transparent violet seal, which is further packed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

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 % *I* 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 **CISPLATIN 50 mg/50 ml OETHMAAN** in contact with injection material that contains aluminium.

DO NOT administer **CISPLATIN 50 mg/50 ml OETHMAAN** undiluted.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

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Johannesburg

2195

8 REGISTRATION NUMBER(S):

57/26/0700

9 DATE OF FIRST AUTHORISATION

Date of registration: 23 January 2024

10 DATE OF REVISION OF THE TEXT

Not applicable