SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Cisplatin 10 mg/10 mL concentrate solution for infusion
Platifirst

2. Qualitative and quantitative composition

Each vial contains 10 mg of cisplatin.
Each mL of concentrate solution contains 1 mg of cisplatin.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Concentrate solution for infusion.

Clear, colourless to pale yellow solution.

4. Clinical particulars

4.1 Therapeutic indications

Like other anticancer drugs, cisplatin is generally used in combination with other approved anticancer drugs as an adjuvant therapy with surgery or radiotherapy and is indicated as palliative therapy for the treatment of:

1. Metastatic testicular tumors
   In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumours who have already received appropriate surgical and/or radiotherapeutic procedures.
2. Metastatic ovarian tumours
   In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumours who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of Cisplatin and cyclophosphamide. Cisplatin, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumours refractory to standard chemotherapy who have not previously received Cisplatin therapy.
3. Advanced bladder cancer
   Cisplatin is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments, such as surgery and/or radiotherapy.

4.2 Posology and method of administration

Patients should be adequately hydrated before and for 24 hours after administration. Various regimens of intravenous administration with or without mannitol and/or frusemide diuresis have been employed. All patients should receive adequate hydration protocols and pre-medication for emesis. Many clinicians recommend the administration of 1 to 2 litres of fluid to be infused over 8 to 12 hours before administration of cisplatin for adults (*if not contraindicated*). IV fluid administration, alone or with mannitol and/or frusemide is infused at a rate sufficient to maintain hydration and diuresis of 150-400 ml/hour during and for at least 4 to 6 hours after cisplatin administration and then at least 100-200 ml/hr for the next 18 to 24 hours, or until vomiting stops and oral fluids are tolerated. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic agents or radiation therapy.

Pre-treatment hydration
In order to prevent renal toxicity, hydration of the patient by infusion of 1 to 2 litres of fluid for 8 to 12 hours prior to treatment is recommended. Adequate hydration must be maintained for 24 hours after a dose. (Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at the discretion of the physician.)

Administration
The requisite drug dose may be diluted in 2 litres of 5% dextrose or 0.9% saline injection containing 18.75 g mannitol/L (37.5g/2 L) and infused IV over 6 to 8 hours. (Rate of administration has varied from a 20 to 30-minute infusion (low dose), 1mg\minute infusion, 6- to 8-hour infusion, 24-hour infusion (medium to high dose) or per-protocol depending upon the dose. (Longer infusion times are preferred to avoid renal toxicity.)

If given as a single-agent therapy, the following dosages may be used. (Refer to the protocol by which the patient is being treated since numerous dosing schedules exist and depend on disease, response and concomitant therapy.)

Adults
Metastatic testicular tumors
The usual cisplatin dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/m^2 IV daily for 5 days per cycle.

Metastatic ovarian tumours
The usual cisplatin dose for the treatment of metastatic ovarian tumours in combination with cyclophosphamide is 75 to 100 mg/m^2 IV per cycle once every 4 weeks (Day 1). The dose of cyclophosphamide when used in combination with cisplatin is 600 mg/m2 IV once every 4 weeks (Day 1).

For directions for the administration of cyclophosphamide, refer to the cyclophosphamide package insert. In combination therapy, cisplatin and cyclophosphamide are administered sequentially.

As a single agent, cisplatin should be administered at a dose of 100 mg/m^2 IV per cycle once every 4 weeks.

Advanced bladder cancer
Cisplatin should be administered as a single agent at a dose of 50 to 70 mg/m^2 IV per cycle once every 3 to 4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m^2 per cycle repeated every 4 weeks is recommended.

Dosage in renal failure
See specific protocol. In general, renal function should have normalised before patients are retreated. A full cisplatin dose can be administered if creatinine clearance is greater than 60ml/min and if the patient can tolerate vigorous hydration. The use of cisplatin should be avoided if creatinine clearance is < 50ml/min. If cisplatin is used in the presence of impaired renal function, reduce the dose as follows:
CrCl 10-50ml/min - give 50%-75% of the dose.
CrCl < 10ml/min: give 25%-50% of dose.

Dosage in hepatic failure
No adjustment is required.

Children
Dosage and safety are not definitively established.

Note
Since cisplatin reacts with aluminium, needles, syringes, catheters or IV administration sets that contain aluminium parts should not be used for administration of cisplatin injection. Any solution with precipitate should be discarded.

4.3 Contraindications
Cisplatin is contraindicated in patients with a history of hypersensitivity to cisplatin or other platinum-containing compounds. It should not be used in pregnancy or lactation. Since cisplatin is nephrotoxic, myelosuppressive and ototoxic, to prevent further additive toxicity, its use in patients with renal or hearing impairment or suppressed bone marrow function should be avoided.

4.4 Special warnings and precautions for use
- Cisplatin is a cytotoxic anticancer drug and hence should be used only by Physicians experienced in handling cancer chemotherapeutic drugs. Great care needs to be exercised in handling the aqueous solution. The personnel carrying out these procedures should be adequately protected with clothing, gloves & and eye shields. In case the solution comes in contact with the skin or mucosae, immediately wash the skin thoroughly with soap and water.
- Cumulative, dose-related renal toxicity is the major dose-limiting toxicity of cisplatin. Renal function must return to acceptable limits before further doses are given. Measurement of BUN, serum creatinine and creatinine clearance should be taken not only before initiating cisplatin therapy but also prior to subsequent courses as well. Hydration and maintenance of high urinary flow during cisplatin therapy may prevent or minimize nephrotoxicity. Aggressive pre-medication with anti-emetics is usually helpful for controlling nausea and vomiting.
- Tinnitus or occasional decreased ability to hear normal conversation indicates ototoxicity. It is more severe in children. Hearing function should be evaluated periodically prior to and also throughout treatment with cisplatin.
- Since myelosuppression, particularly thrombocytopenia (WBC: mild, Platelets: mild, Onset (days): 10, Nadir (days): 14-23, Recovery (days): 21-39) may occur in patients treated with cisplatin, subsequent courses of cisplatin should not be given until platelets are present at levels greater than 100,000 cells/mm3 and WBCs greater than 4000cells/mm^3.
- Anaphylactic reactions to cisplatin have been reported, occurring within minutes of administration in patients with prior exposure to cisplatin, and can be alleviated by administration of epinephrine, steroids and antihistamines.
- Hypomagnesemia and hypocalcaemia occur with cisplatin administration. It does not appear to be dose-related. However, monitoring of electrolytes is necessary.
- Peripheral neuropathy and postural hypotension may occur. It appears to be more common with prolonged administration of cisplatin. Neurological examinations should be performed regularly.
- Liver function should be monitored periodically.
- Visual impairment, hypersensitivity and seizures are rarely observed.

4.5 Interaction with other medicinal products and other forms of interaction
Potentially nephrotoxic or ototoxic drugs, e.g., aminoglycoside antibiotics and loop diuretics may potentiate the nephrotoxic and ototoxic effects of cisplatin. Therefore, concomitant administration of such drugs with cisplatin should be avoided. Plasma levels of anticonvulsant agents may become sub-therapeutic during cisplatin therapy. Cisplatin may result in hyperuricemia and gout when concomitantly administered with anti-gout agents such as allopurinol, colchicine or probenecid.

4.6 Pregnancy and lactation
Cisplatin is mutagenic in bacteria. Animal studies show it to be teratogenic and embryo-toxic in mice. Therefore, administration of cisplatin to pregnant women may cause potential harm to the foetus. Hence cisplatin is contraindicated in pregnancy. Cisplatin gets rapidly distributed into the tissues. Since it also gets secreted in breast milk, mothers on cisplatin therapy should not breastfeed.

4.7 Effects on the ability to drive and use machines
No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Side effects	**>10%**
Gastrointestinal Emetic potential	Nausea and vomiting Moderately high (60% to 90%), high (>90%)
Myelo suppression (mainly Thrombocytopenia)	Mild with moderate doses, mild to moderate with high-dose therapy
Neurotoxicity	Peripheral neuropathy
Ototoxicity	High-frequency hearing loss
Miscellaneous	Elevation of liver enzymes, mild alopecia

Side effects	**<1%**
Anaphylactic reaction	Facial oedema, wheezing, tachycardia and hypotension
Local	Phlebitis
Dermatologic Endocrine and metabolic	Mild alopecia syndrome of inappropriate ADH secretion
Ocular	Optic neuritis, blurred vision, papilledema
Cardiovascular	Bradycardia, arrhythmias
Nephrotoxicity	(28 % to 36 %) impairment renal function
Miscellaneous	Mouth sores

*Cisplatin is an irritant & extravasation should be avoided. Thrombophlebitis & tissue damage may occur following infiltration of the drug.

*Sodium thiosulfate may be used as an antidote in case of Cisplatin extravasation, although other institutional policies may exist.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
Symptoms of overdosage with cisplatin include kidney failure, severe myelosuppression, intractable nausea and vomiting, severe neurosensorial toxicities, liver failure etc. Death may also occur. There is no established antidote for cisplatin overdose, and the treatment is largely supportive. Patients should be monitored for 3-4 weeks in case of delayed toxicity. Haemodialysis, even if initiated within 4 hours following overdose is of little help and appears to have little impact on removing platinum from the body because of the high protein binding. Limited experience suggests that plasmapheresis may be useful in removing protein-bound platinum and ameliorating toxicity. Haemodialysis may be required for the management of renal failure.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 9.4 Miscellaneous cytotoxic agents.

Mechanism of Action
Cisplatin inhibits DNA synthesis by the formation of DNA intra-strand and inter-strand cross-links, which denatures the double helix. The cis-isomer is more cytotoxic. The selective toxicity could be due to the fact that the cross-linked DNA adduct is less easily recognized by the repair enzymes of the cell. Cisplatin also inhibits RNA and protein synthesis. Cisplatin activity is cell cycle non-specific.

5.2 Pharmacokinetic properties

Distribution
Cisplatin is rapidly distributed into tissue following administration, found in high concentration in the kidneys, liver, ovaries, uterus and lungs. Protein binding >90 %.

Metabolism
Cisplatin undergoes non-enzymatic metabolism. The drug is inactivated (in both the cell and the bloodstream) by sulfhydryl groups and cisplatin covalently binds to glutathione and thiosulfate.

Elimination
>90 % in urine and 10 % in bile.

Half-life
Initial: 20-30 minutes, Beta: 1 hour, Terminal: approximately 24 hours.

Secondary half-life
44-73 hours.

5.3 Preclinical safety data
Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. Cisplatin may be toxic to the foetal urogenital tract.

6. Pharmaceutical particulars

6.1 List of excipients
Mannitol
Sodium chloride
Hydrochloric acid
Water for injection

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C. Protect from light.

6.5 Nature and contents of the container
A clear USP type I amber glass vial closed with a grey butyl serum rubber stopper and an aluminium flip-off seal.

Fill volume: 10 ml.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
VHB Medi Sciences Limited
Plot No. - 20-22 & 49-51, IIE, Sector-5, Sidcul
Pant Nagar - 263145
Uttarakhand
India

8. MANUFACTURER
VHB Medi Sciences Limited
50-AB Govt. Industrial Estate, Charkop
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9. REGISTRATION DETAILS

Zimbabwe registration number: 2023/9.4/6414
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT

September 2023