SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

PLATIFIRST (Cisplatin 10 mg/10 ml injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1.0 mg cisplatin BP

Excipient(s) with known effect:

Each 10 ml contains 9.00mg sodium chloride

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Liquid Injection

A clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cisplatin Injection is indicated as therapy to be employed as follows:

Metastatic Testicular Tumors: In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures.

Metastatic Ovarian Tumors: In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors 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 tumors refractory to standard chemotherapy who have not previously received Cisplatin Injection therapy.

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

Posology

Cisplatin is administered by slow intravenous infusion. CISPLATIN SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION.

Note: Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin, causing precipitate formation and a loss of potency.

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 Tumors

The usual cisplatin dose for the treatment of metastatic ovarian tumors 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/ m^2 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.

All Patients

Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a cisplatin dose is recommended. The drug is then diluted in 2 liters of 5% Dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol, and infused over a 6- to 8-hour period. If diluted solution is not to be used within 6 hours, protect solution from light. Do not dilute cisplatin in just 5% Dextrose Injection. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of cisplatin should not be given until the serum creatinine is below 1.5 mg/100 mL, and/or the BUN is below 25 mg/100 mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets $\geq$ 100,000/mm^3, WBC $\geq$

4,000/mm^3). Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

Preparation of Intravenous Solutions

Preparation Precautions

Caution should be exercised in handling the aqueous solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing cisplatin.

Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water. More information is available in the references listed below.

Instructions for Preparation

The aqueous solution should be used intravenously only and should be administered by IV infusion over a 6- to 8-hour period.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

NOTE TO PHARMACIST: Exercise caution to prevent inadvertent cisplatin overdosage. Please call prescriber if dose is greater than 100 mg/m^2 per cycle. Aluminum and flip-off seal of vial have been imprinted with the following statement:

CALL DR. IF DOSE > 100 MG/M /CYCLE.

4.3 Contraindications

Cisplatin is contraindicated in patients with pre-existing renal impairment. Cisplatin should not be employed in myelosuppressed patients, or in patients with hearing impairment.

Cisplatin is contraindicated in patients with a history of allergic reactions to cisplatin or other platinum containing compounds.

4.4 Special warnings and precautions for use

WARNING
Cisplatin should be administered under the supervision of a qualified physician

experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Cumulative renal toxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea, and vomiting.

Ototoxicity, which may be more pronounced in children, and is manifested by tinnitus, and/or loss of high frequency hearing and occasionally deafness, is significant.

Anaphylactic-like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of cisplatin administration. Epinephrine, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms.

Exercise caution to prevent inadvertent cisplatin overdose. Doses greater than 100 mg/m^2/cycle once every 3 to 4 weeks are rarely used. Care must be taken to avoid inadvertent cisplatin overdose due to confusion with carboplatin or prescribing practices that fail to differentiate daily doses from total dose per cycle.

WARNINGS:

Cisplatin produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, blood urea nitrogen (BUN), creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, cisplatin should not be given more frequently than once every 3 to 4 weeks. Elderly patients may be more susceptible to nephrotoxicity.

There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of cisplatin or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. Elderly patients may be more susceptible to peripheral neuropathy.

Loss of motor function has also been reported.

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 epinephrine, corticosteroids, and antihistamines.

Cisplatin can commonly cause ototoxicity which is cumulative and may be severe. Audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug.

All pediatric patients receiving cisplatin should have audiometric testing at baseline, prior to each subsequent dose of drug and for several years post therapy.

Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant.

The carcinogenic effect of cisplatin was studied in BD IX rats. Cisplatin was administered intraperitoneally (i.p.) to 50 BD IX rats for 3 weeks, 3 x 1 mg/kg body weight per week. Four hundred and fifty-five days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma.

The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

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. A specific treatment for extravasation reactions is unknown at this time.

PRECAUTIONS:

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly.

4.5 Interaction with other medicinal products and other forms of Interaction

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.

In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

Nursing Mothers

Cisplatin has been reported to be found in human milk; patients receiving cisplatin should not breastfeed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. All children should have audiometric monitoring performed prior to initiation of therapy, prior to each

subsequent dose, and for several years post therapy. Advanced testing methods may allow for earlier detection of hearing loss in an attempt to facilitate the rapid initiation of interventions that can limit the potential adverse impact of hearing impairment on a child's cognitive and social development.

Geriatric Use

Insufficient data are available from clinical trials of cisplatin in the treatment of metastatic testicular tumors or advanced bladder cancer to determine whether elderly patients respond differently than younger patients. In four clinical trials of combination chemotherapy for advanced ovarian carcinoma, 1,484 patients received cisplatin either in combination with cyclophosphamide or paclitaxel. Of these, 426 (29%) were older than 65 years. In these trials, age was not found to be a prognostic factor for survival. However, in a later secondary analysis for one of these trials, elderly patients were found to have shorter survival compared with younger patients. In all four trials, elderly patients experienced more severe neutropenia than younger patients. Higher incidences of severe thrombocytopenia and leukopenia were also seen in elderly compared with younger patients, although not in all cisplatin containing treatment arms. In the two trials where nonhematologic toxicity was evaluated according to age, elderly patients had a numerically higher incidence of peripheral neuropathy than younger patients. Other reported clinical experience suggests that elderly patients may be more susceptible to myelosuppression, infectious complications, and nephrotoxicity than younger patients.

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

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of cisplatin in pregnant women, but based on its pharmacological properties Cisplatin is suspected to cause serious birth defects. Studies in animals have shown reproductive toxicity and transplacental carcinogenicity. Cisplatin is contraindicated during the pregnancy period.

Breast-feeding

Cisplatin is excreted in human milk. Breastfeeding during the therapy is contraindicated.

Fertility

BOTH MALE AND FEMALE PATIENTS MUST USE EFFECTIVE CONTRACEPTIVE METHODS TO PREVENT CONCEPTION AND/OR REPRODUCTION DURING AND FOR AT LEAST 6 MONTHS AFTER TREATMENT WITH CISPLATIN. Genetic consultation is recommended if the patient wishes to have children after ending the 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 cryoconservation of their sperm prior to the treatment.

4.7 Effects on ability to drive and use machines

Due to the possible side effects cisplatin has minor or moderate influence on the ability to drive and use machines. Patients who suffer from these effects (eg feeling sleepy or vomiting) must avoid driving and operating machinery.

4.8 Undesirable effects

Nephrotoxicity

Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose limiting toxicity of cisplatin. Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. **Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dos e of cisplatin can be given.** Elderly patients may be more susceptible to nephrotoxicity.

Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6- to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz). The prevalence of hearing loss in children is particularly high and is estimated to be 40 to 60%. Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Ototoxic effects may be more severe in children receiving cisplatin.

Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated cisplatin doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Ototoxicity can occur during treatment or be delayed. Audiometric monitoring should be performed prior to initiation of therapy, prior to each subsequent dose, and for several years post therapy.

The risk of ototoxicity may be increased by prior or simultaneous cranial irradiation, and may be more severe in patients less than 5 years of age, patients being treated with other ototoxic drugs (e.g., aminoglycosides and vancomycin), and in patients with renal impairment.

Genetic factors (e.g., variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.

Hematologic

Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression.

In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Gastrointestinal

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment.

Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea has also been reported.

OTHER TOXICITIES:

Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic-uremic syndrome [HUS]), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Serum Electrolyte Disturbances

Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin.

Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia

Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine.

It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity

Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic

symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy.

Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported.

Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) have also been reported.

Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity

Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established.

Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions

Anaphylactic-like reactions have been reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity

Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

Other Events

Cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, asthenia, and dehydration have been reported.

Local soft tissue toxicity has been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.

4.9 Overdose

Caution should be exercised to prevent inadvertent overdosage with cisplatin. Acute overdosage with this drug may result in kidney failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, intractable nausea and vomiting and/or neuritis. In addition, death can occur following overdosage.

No proven antidotes have been established for cisplatin overdosage. Hemodialysis, even when initiated four hours after the overdosage, appears to have little effect on removing platinum from the body because of cisplatin's rapid and high degree of protein binding. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that may occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Other Antineoplastic agents/Platinum compounds;

ATC code: L01XA01

Mechanism of Action

Cisplatin is an inorganic substance containing a heavy metal [cis-diamminedichloroplatinum(II)]. This substance inhibits the DNA synthesis by realising transverse connections within and between the DNA strings. The protein and RNA synthesis is inhibited to a lesser extent.

Pharmacodynamic effects

Although the primary activity of cisplatin seems to be the inhibition of DNA synthesis, the antineoplastic process includes other activities, such as enlargement of the tumour

immunogenicity. Cisplatin's oncolytic functions can be compared to the functions of alkylating substances. Cisplatin also offers immunosuppressive, radiosensitising and antibacterial features.

Cisplatin does not seem to be cell cycle specific.

The cytotoxic activities of cisplatin are caused by binding all DNA bases, with a preference for the N-7 position of guanine and adenosine.

5.2 Pharmacokinetics:

Distribution

After intravenous administration, cisplatin is rapidly distributed among all tissues. Following cisplatin doses of 20 to 120 mg/m^2, the concentrations of platinum are highest in liver, prostate and kidney, somewhat lower in bladder, muscles, testicle, pancreas and spleen and lowest in bowel, adrenal, heart, lung, cerebrum and cerebellum.

Biotransformation

Over 90% of the total plasma cisplatin is bounded with protein after two hours following the administration. This process may be irreversible. The protein-bounded part is not antineoplastic active. Cisplatin is non-linearly pharmacokinetic. Cisplatin is converted by a non-enzymatic process into one or more metabolites. Elimination from the plasma is realised in two phases after intravenous bolus injection of 50-100 mg/m^2 of cisplatin. The following half-life period have been registered for humans:

t ½ (distribution): 10-60 minutes

t ½ (terminal): approximately 2-5 days

Elimination

The considerable protein binding of the total platinum contents results in an extended or incomplete excretion phase with cumulative urine secretion ranging from 27 to 45% of the administered dose in a period from 84 to 120 hours. An extended infusion results in the urine secretion of a larger part of the dose. The faecal secretion is minimal, and small amounts of platinum can be traced in the gallbladder and the large intestine. Dysfunctional kidneys increase the plasma half-life period, which may also increase theoretically in the presence of ascites caused by the highly protein binding activities of cisplatin.

5.3 Preclinical safety data

Chronic toxicity:

Chronic toxicity models indicate kidney damage, bone marrow depression, gastro-intestine disorders and ototoxicity.

Mutagenity and carcinogenity:

Cisplatin is mutagenic in numerous *in vitro* and *in vivo* tests (bacterial test systems and chromosome defects in animal cells and tissue cultures). Long term studies of cisplatin on mice and rats evidenced the carcinogenic effects.

Reproductive toxicity:

Fertility: Gonadal suppression resulting in amenorrhoea or azoospermia may be irreversible and cause definitive infertility.

Studies in rats showed that exposure during pregnancy produces tumours in the adult offspring.

Pregnancy and lactation: Cisplatin is embryotoxic and teratogenic for mice and rats, and defects have been reported for both species. Cisplatin was found in the milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Hydrochloric Acid

Water for Injections

6.2 Incompatibilities

Cisplatin reacts with aluminium which results in production of a black platinum precipitate. Therefore, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided.

This medicinal product must not be mixed with other medicinal products.

The cisplatin 1 mg/ml concentrate must not be diluted with glucose solution 5% alone or mannitol solution 5% alone, but only with the mixtures containing additionally sodium chloride.

Antioxidants (such as sodium metabisulphite), bicarbonates (sodium bicarbonate), sulfates, fluorouracil and paclitaxel may inactivate cisplatin in infusion systems.

6.3 Shelf life

24 Months

6.4 Special Precaution for storage

Store below 30℃. Protected from light. Do not refrigerate.

6.5 Nature and contents of container

10 ml Amber Moulded Glass vial closed with 20 mm rubber stopper and sealed with 20mm flip off aluminium seal is placed in a carton and pack insert.

6.6 Special precautions for disposal and other handling

Cisplatin 1 mg/ml concentrate for solution for infusion is to be diluted before use. For preparation of solution for infusion, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided.

Preparation of solution for infusion must take place in aseptic conditions.

For dilution of the concentrate, one of the following solutions should be used:

- sodium chloride solution 0.9%;
- mixture of sodium chloride solution 0.9% and glucose solution 5% (1:1) (resulting final concentrations: sodium chloride 0.45%, glucose 2.5%).
- Should hydration prior to the treatment with cisplatin be impossible, the concentrate may be diluted with:
- mixture of sodium chloride solution 0.9% and mannitol solution 5% (1:1) (resulting final concentrations: sodium chloride 0.45%, mannitol 2.5%).

Preparation of cisplatin solution for infusion:

The required amount (dose) of the cisplatin concentrate 1 mg/ml calculated according to the instructions should be diluted in 1-2 litres of one of the above mentioned solutions.

The diluted solution should be administered only by intravenous infusion.

Only clear and colourless to yellowish solutions without visible particles should be used.

For single use only.

Cytotoxic agents should be prepared for administration only by personnel who have been trained in the safe handling of the preparation.

Refer to local cytotoxic handling guidelines.

As any other cytotoxic agent, cisplatin should be used with extreme caution: gloves, face masks and protective clothing are required and vital. Cisplatin should be processed under a protective hood, if possible. Contact with skin and/or mucous membranes must be avoided. Pregnant hospital employees should not work with cisplatin.

Skin contact: Rinse with large quantities of water. Apply an ointment if you have a temporary burning feeling. (Note: Some persons are sensitive to platinum and may experience a skin reaction).

In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and seal it. In the case of spillage all items coming into contact with Cisplatin should be handled and disposed in accordance to local cytotoxic guidelines.

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

7. MARKETING AUTHORIZATION HOLDER

M/S VHB MEDI SCIENCES LTD.
50 AB, Govt industrial Estate,
Charkop, Kandivali (W)
Mumbai-400067, INDIA

Manufacturing site:

VHB MEDI SCIENCES LTD.
Plot No.20-22 & 49-51, IIE, Sector-5,
SIDCUL, Pantnagar, Udham Singh Nagar,
Uttarakhand, INDIA.

8. MARKETING AUTHORIZATION NUMBER

06001/07387/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

13/07/2022

10. DATE OF REVISION OF THE TEXT

18/07/2023