CISPLASOL
(Cisplatin)

1. NAME OF THE MEDICINAL PRODUCT

CISPLASOL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 or 50 mL vials containing 10 or 50 mg cisplatin freeze dried powder for injection.

3. PHARMACEUTICAL FORM

Freeze dried powder for injection

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

CISPLASOL (cisplatin) has been shown to produce significant responses in a number of malignancies. The drug, mainly in combination chemotherapeutic regimens, is commonly used for the treatment of the following solid malignancies:

- *Testicular tumors* (including extragonadal germ-cell tumors)
- *Ovarian carcinoma*
- *Lung cancer* (both small and non-small cell carcinoma)
- *Head and neck cancer*

In addition, CISPLASOL (cisplatin) has been shown to possess antitumor activity in the following tumors:

- *Uterine cervix cancer*
- *Bladder cancer*
- *Osteosarcoma*
- *Melanoma*
- *Neuroblastoma*
- *Oesophageal carcinoma*

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

CISPLASOL (cisplatin) can be given either as a single agent or in combination with other antiproliferative drugs. A variety of doses and schedules are used. To obtain optimum therapeutic results with minimum adverse effects, the dosage of CISPLASOL (cisplatin) must be based on the clinical, renal and hematologic status of the patient. Usual doses when the drug is given intravenously as a single agent (to both adults and children) range from 50 to 120 mg/m² by I.V. infusion over 6 to 8 hours once every 3-4 weeks according to the tumor type and the patient's status (including renal function and the extent of

any previous radiation therapy and/or chemotherapy), or 15 to 20 mg/m²/day by I.V. infusion over five consecutive days, to be repeated every 3-4 weeks. When the drug is given in combination with other cytotoxic compounds, these dosages may have to be adjusted employing doses from 20 mg/m² upwards every 3-4 weeks.

Although CISPLASOL (cisplatin) is usually administered intravenously; the drug has also been given by intraperitoneal instillation to patients with intraperitoneal malignancies (e.g., ovarian tumors). Steep concentration gradients between intraperitoneal and plasma drug levels can be achieved by this route of administration.

CISPLASOL (cisplatin) powder should be dissolved in water to give a final concentration of 1 mg/mL. Reconstitution as recommended results in a clear, colourless solution (Section 6.5).

Aluminium containing equipment should not be used for administration of CISPLASOL (cisplatin).

4.3. CONTRAINDICATIONS

Cisplatin is contra-indicated in patients who have previously experienced allergic reactions to cisplatin or other platinum-containing compounds, and in the presence of severe renal impairment and generalized infections.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cisplatin is a highly toxic drug with a relatively narrow therapeutic index, and a therapeutic effect is unlikely to occur without some evidence of toxicity. Therefore, it is recommended that cisplatin be administered to patients in a hospital setting under supervision of a physician experienced in cancer chemotherapy.

Special warnings apply to the following areas.

- *Renal function*. Cisplatin produces cumulative nephrotoxicity. Renal function and serum electrolyte (magnesium, sodium, potassium and calcium) should be evaluated prior to initiating cisplatin treatment and prior to each subsequent course of therapy. To maintain urine output and reduce renal toxicity it is recommended that cisplatin be administered as an intravenous infusion over 6 to 8 hours (Section 4.2). Moreover, pre-treatment intravenous hydration with 1-2 liters of fluid over 8-12 hours followed by adequate hydration for the next 24 hours is recommended.

Repeat courses of cisplatin should not be given unless the level of serum creatinine is below 1.5 mg/100 mL or the BUN is below 25 mg/100 mL.

Special care has to be taken when cisplatin-treated patients are given concomitant therapies with other potentially nephrotoxic drugs (Section 4.5).

- *Bone marrow function.* Peripheral blood counts should be monitored frequently in patients receiving cisplatin. Although the hematologic toxicity is usually moderate and reversible, severe thrombocytopenia and leukopenia may occur. In patients who develop thrombocytopenia special precautions are recommended: care in performing invasive procedures; search for signs of bleeding or bruising; test of urine, stools and emesis for occult blood; avoiding aspirin and other NSAIDs.

Patients who develop leukopenia should be observed carefully for signs of infection and might require antibiotic support and blood product transfusions.

- *Hearing function*. Cisplatin may produce cumulative ototoxicity, which is more likely to occur with high-dose regimens. Audiometry should be performed prior to initiating therapy, and repeated audiograms should be performed when auditory symptoms occur or clinical hearing changes become apparent. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. Cases of delayed-onset hearing loss have been reported in the pediatric population. Long term follow-up in this population is recommended.[2]

- *CNS functions*. Cisplatin is known to induce neurotoxicity; therefore, neurologic examination is warranted in patients receiving a cisplatin-containing treatment. Since neurotoxicity may result in irreversible damage, it is recommended to discontinue therapy with cisplatin when neurologic toxic signs or symptoms become apparent.

In addition, patients receiving cisplatin should be observed for possible anaphylactoid reactions, and appropriate equipment and medication should be readily available to treat such reactions.

- *Immunosuppressant effects/Increased susceptibility to infections.* Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cisplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cisplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Cisplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. In these circumstances additive toxicity is likely to occur.

Other known drug interactions are reported below.

- *Nephrotoxic drugs*. Aminoglycoside antibiotics, when given concurrently or within 1-2 weeks after cisplatin administration, may potentiate its nephrotoxic effects. Concomitant use of other potentially nephrotoxic drugs (e.g., amphotericin B) is not recommended during cisplatin therapy. The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients who have previously been given cisplatin.[2]

- *Ototoxic drugs*. Concurrent and/or sequential administration of ototoxic drugs such as aminoglycoside antibiotics or loop diuretics may increase the potential of cisplatin to cause ototoxicity, especially in the presence of renal impairment. Ifosfamide may increase hearing loss due to cisplatin.[2]

- *Renally excreted drugs*. Literature data suggest that cisplatin may alter the renal elimination of bleomycin and methotrexate (possibly as a result of cisplatin-induced nephrotoxicity) and enhance their toxicity. Reduction of the lithium blood levels was noticed in a few cases after treatment with cisplatin combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium values.[2]

- *Anticonvulsant agents*. Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.[2] In patients receiving cisplatin 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 antiepileptics should be monitored and dosage adjustments made as necessary.

- *Antigout agents*. Cisplatin may raise the concentration of blood uric acid. Thus, in patients concurrently receiving antigout agents such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricemia and gout.

- *Anticoagulants.* It is advisable to check the INR when oral anticoagulants such as coumarins/warfarin are used simultaneously with cisplatin.[2]

- *Paclitaxel.* Administration of cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and can therefore intensify neurotoxicity.[2]

4.6. FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during treatment with cisplatin and for at least 26 weeks following the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with cisplatin and for at least 14 weeks after the last dose.[2]

For patients with end-stage renal disease, the washout period of cisplatin will be longer (up to 7 weeks); effective contraception for men is advised for at least 19 weeks and for female patients, for at least 31 weeks after the last dose.[2]

Pregnancy

The safety of cisplatin in pregnancy has not been established. Cisplatin can cross the placental barrier. Cisplatin has been shown to be teratogenic, embryotoxic and carcinogenic in mice and rats and leukemogenic in rats (Section 5.3). Therefore, cisplatin is considered to be potentially harmful to the foetus when administered to a pregnant woman. If the drug is administered during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant during cisplatin therapy.

Males undergoing cisplatin treatment should use barrier contraceptive measures.

Lactation

Limited data from published literature report presence of cisplatin in human milk. Advise pregnant women not to breastfeed during treatment with cisplatin.[2]

Fertility

Female
Based on non-clinical (Section 5.3) and clinical findings, female fertility may be compromised by treatment with cisplatin. Use of cisplatin has been associated with cumulative dose-dependent ovarian failure, premature menopause and reduced fertility.[2]

Male
Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported (Section 4.8). Although the impairment of spermatogenesis can be reversible, males undergoing cisplatin treatment should be warned about the possible adverse effects on male fertility.[2]

Both men and women should seek advice on fertility preservation before treatment.[2]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of cisplatin on the ability to drive and use machinery has not been systematically evaluated.

4.8. UNDESIRABLE EFFECTS

Blood and lymphatic system disorders: Myelosuppression often occurs during cisplatin therapy, but is mostly mild to moderate and reversible at the usual doses. However, leukopenia and thrombocytopenia are dose-related, and may become clinically relevant in patients receiving high doses of cisplatin or in patients who have received prior myelosuppressive treatments. WBC and platelet nadirs generally occur after about 2 weeks but levels return to pre-treatment values in most patients within 4 weeks. Cisplatin may also induce anaemia: this is not clearly dose-related and is occasionally caused by hemolysis.

There have been rare reports of acute myelogenous leukemias and myelodysplastic syndromes arising in patients who have been treated with cisplatin, mostly when given in combination with other potentially leukemogenic agents.

Immune system disorders: Anaphylactic and anaphylactic-like reactions, such as flushing, facial edema, wheezing, tachycardia and hypotension, have been occasionally reported. These reactions may occur within minutes of cisplatin administration.

Metabolism and nutrition disorders: Cisplatin may also cause serious electrolyte disturbances, mainly represented by hypomagnesemia, hypocalcemia, and hypokalemia, and associated with renal tubular dysfunction. Hypomagnesemia and/or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm, and/or tetany. Other reported toxicities are hyperuricemia, hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH).

Nervous system disorders: Peripheral neuropathies occur infrequently with usual doses of the drug. These are generally sensory in nature (e.g., paresthesia of the upper and lower extremities) but can also include motor difficulties, reduced reflexes and leg weakness. Autonomic neuropathy, seizures, slurred speech, loss of taste and memory loss have also been reported. These neuropathies usually appear after prolonged therapy, but have also developed after a single drug dose. Peripheral neuropathy may be irreversible in some patients; however, it has been partially or completely reversible in others following discontinuance of cisplatin therapy. Cerebrovascular accident has been reported in patients treated with cisplatin. Lhermitte's sign has been reported.[2]

Eye disorders: Optic neuritis, papilledema, and cortical blindness have been reported rarely in patients receiving cisplatin. These events are usually reversible after drug withdrawal.

Ear and labyrinth disorders: Unilateral or bilateral tinnitus, with or without hearing loss, occurs in about 10% of cisplatin-treated patients and is usually reversible. The damage to the hearing system appears to be dose-related and cumulative, and it is reported more frequently in very young and very old patients.

Cardiac disorders: Cardiovascular abnormalities (coronary artery disease, congestive heart failure, arrhythmias, postural hypotension, thrombotic microangiopathy, etc.).

Vascular disorders: Venous thromboembolism[1]

Respiratory, thoracic and mediastinal disorders: Pulmonary toxicity has been reported in patients treated with cisplatin in combination with bleomycin or 5-fluorouracil.

Gastrointestinal disorders: Nausea and vomiting occur in the majority of cisplatin-treated patients, usually starting within 1 hour of treatment and lasting up to 24 hours or longer. These side effects are only partially relieved by standard antiemetics. The severity of these symptoms may be reduced by dividing the total dose per cycle into smaller doses given once daily for five days. Reported toxicity includes gingival platinum line.

Hepatobiliary disorders: Mild and transient elevations of serum AST and ALT levels may occur infrequently.

Skin and subcutaneous tissue disorders: Mild alopecia. Rarely, urticarial or maculopapular skin rashes have also been observed.

Musculoskeletal and connective tissue disorders: Myalgia

Renal and urinary disorders: Acute renal toxicity, which was highly frequent in the past and represented the major dose-limiting toxicity of cisplatin, has been greatly reduced by the use of 6 to 8-hour infusions as well as by concomitant intravenous hydration and forced diuresis. Cumulative toxicity, however, remains a problem and may be severe. Renal impairment, which is associated with tubular damage, may be first noted during the second week after a dose and is manifested by an increase in serum creatinine, BUN, serum uric acid and/or a decrease in creatinine clearance. Renal insufficiency is generally mild to moderate and reversible at the usual doses of the drug (recovery occurring as a rule within 2-4 weeks); however, high or repeated cisplatin doses can increase the severity and duration of renal impairment and may produce irreversible renal insufficiency (sometimes fatal). Renal failure has been reported also following intraperitoneal instillation of the drug.

Reproductive system and breast disorders: Impairment of spermatogenesis and azoospermia have been reported.

General disorders and administration site conditions: pyrexia, local effects such as phlebitis, cellulitis and skin necrosis (following extravasation of the drug) may also occur.

4.9. OVERDOSE

Acute overdosage with cisplatin may result in an enhancement of its expected toxic effects (e.g., kidney failure, severe myelosuppression, intractable nausea and vomiting, severe neurosensorial toxicities, liver failure etc.). Death may also occur.

No proven antidotes are known for cisplatin overdosage. Hemodialysis is only effective, even then partially, up to 3 hours after administration because of the rapid and extensive binding of platinum to plasma proteins. Signs and symptoms of overdosage should be managed with supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Cisplatin is a platinum-containing antineoplastic agent. Although its mechanism of action has not been conclusively determined, it is thought to act similarly to bifunctional alkylating agents i.e., by possible cross-linking and interference with the function of DNA. The primary pharmacodynamic effect of cisplatin is represented by inhibition of cell growth, which appears to be cycle and phase non-specific. Besides tumour cells, the target tissues are mainly those characterised by rapid cell proliferation such as bone marrow, gastrointestinal mucosa and gonads.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Cisplatin is usually administered by the intravenous route, and preferably by IV infusion over 6-8 hours. During conventional IV infusions, plasma levels of total platinum increase gradually and peak at the end of the infusion.

Distribution

Platinum is widely distributed into body fluids and tissues, with the highest concentrations in the kidneys, liver and prostate. Cisplatin and its platinum containing metabolites are rapidly and extensively bound to tissue and plasma proteins, including albumin, gamma-globulin and transferrin. Three hours after a bolus injection and two hours after the end of a three hour infusion 90% of the plasma platinum is protein-bound. Following repeated treatment courses, platinum appears to accumulate in body tissues and has been detected in some tissues for up to 6 months after the last dose of the drug.

Metabolism

The metabolic fate of cisplatin has not been completely elucidated. Biotransformation occurs by rapid nonenzymatic conversion to inactive metabolites, which have not been definitely identified.

Excretion

Studies aiming at determining plasma elimination half-life of total platinum have shown a very large interindividual and interstudy variation: 2 to 72 hours in normal subjects, and 1 to 240 hours in end-stage renal disease. Excretion occurs mainly through the kidneys. The effects of renal impairment on the elimination of cisplatin and its platinum-containing products have not been fully evaluated. Cisplatin may be

eliminated from the systemic circulation by dialysis, but only within 3 hours after administration and to a limited extent.

Relationships between plasma concentrations of cisplatin or platinum and therapeutic activity or clinical toxicity have not been clearly established. However, results of *in vitro* studies have suggested that only non-protein-bound cisplatin or its platinum-containing products are cytotoxic. There is also some evidence that patients with impaired renal function may have elevated plasma levels of non-protein-bound platinum.

5.3. PRECLINICAL SAFETY DATA

In repeat dose toxicity models, renal damage, bone marrow depression, gastrointestinal disorders, ototoxicity, neurotoxicity, and immunosuppression have been observed.

Cisplatin is mutagenic in numerous *in vitro* and *in vivo* tests. In long term studies, it has been shown that cisplatin is carcinogenic in mice and rats.

Non-clinical findings in mice showed that cisplatin caused direct damage to primordial follicle oocytes, leading to apoptosis, and ovarian depletion. Cisplatin causes testis damage and decreased sperm counts in mice, primarily through effects on differentiated spermatogonia. These findings suggest potential effects on male and female fertility.[2,3]

Cisplatin is embryotoxic in mice and rats, and in both species, deformities have been reported.[3]

Studies in rodents have shown that exposure during pregnancy can cause tumors in adult offspring.[3]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Mannitol
Sodium Chloride
qs: Water for Injections
qs pH adjustment Ph Eur: Sodium Hydroxide (2M), Hydrochloric Acid (2M),
qs To purge vials Ph Eur: Nitrogen

6.2. SHELF LIFE

24 months
The reconstituted solution must be used within 24 hours. It should be kept at room temperature and protected from light, also during I.V. infusion.

6.3. SPECIAL PRECAUTIONS FOR STORAGE

The unopened vials should be stored at controlled room temperature, protected from light.

The reconstituted solution must not be cooled or refrigerated as cooling may result in precipitation; it should be kept at room temperature and protected from light, also during I.V. infusion.

Any unused solution should be discarded.

6.4. NATURE AND CONTENTS OF CONTAINER

CISPLASOL (cisplatin) Injection: 10 mg in 10 mL, 50 mg in 50 mL

6.5. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCT AND OTHER HANDLING OF THE PRODUCT

Cisplatin powder should be dissolved in sterile Water for Injection such that the reconstituted solution contains 1 mg/mL of cisplatin. The reconstituted solution should be diluted in 2 liters of 0.9% Sodium Chloride Injection or 5% Dextrose and 0.45% Sodium Chloride Solution (to which 37.5 g of mannitol may be added).

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with cisplatin.
- Preparation should be performed in a designated area ideally in a vertical laminar flow hood, with the work surface covered with disposable plastic-backed absorbent paper.
- Care should be taken to prevent inhaling particles and exposing the skin to cisplatin.
- Adequate protective clothing should be worn, such as PVC gloves, safety glasses, disposable gowns and masks.
- It is recommended that luer lock fittings are used in the assembly of syringes and giving sets to avoid leakage.
- In the event of contact with the eyes, wash with water or saline; if the skin comes into contact with the drug wash thoroughly with water and in both cases seek medical advice. Seek immediate medical attention if the drug is ingested or inhaled.
- All used material, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be incinerated. Excreta should be similarly treated. Contaminated surfaces should be washed with copious amounts of water.

Cisplasol/LPD/PK-03
According to CDS V 3.0 dated: 21 January 2021; Supersedes CDS V 2.0 dated: 18 November 2019

Marketed by:
Pfizer Pakistan Limited

Please visit our website www.pfizerpro.com.pk for latest version of Product leaflet.

7. REFERENCES

1. Module 2.5 Clinical Overview, Addition of the Adverse Drug Reaction - Venous Thromboembolism Under Section 4.8 Undesirable Effects of the Core Data Sheet, June 2016.

2. Module 2.5 Clinical Overview, To Support the Updates to Sections 4.4, 4.5, 4.6, 4.8, and 5.3 of the Core Data Sheet, November 2019.

3. Module 2.4 Nonclinical Overview, To Support the Updates to Sections 4.6 and 5.3 of the Core Data Sheet, December 2020.