Summary of Product Characteristics

1. Name of the medicinal product

PLATIFIRST (Cisplatin Injection BP 50mg/50mL)

2. Qualitative and Quantitative Composition

Each mL contains;
Cisplatin…….1.0 mg
Water for injection……..q.s

3. Pharmaceutical form

Description: A clear, colourless to pale yellow solution.

4. Clinical Particulars

4.1 Therapeutic indications

Cisplatin is intended for the treatment of:

- advanced or metastasised testicular cancer
- advanced or metastasised ovarian cancer
- advanced or metastasised bladder carcinoma
- advanced or metastasised squamous cell carcinoma of the head and neck
- advanced or metastasised non-small cell lung carcinoma
- advanced or metastasised small cell lung carcinoma

Cisplatin is indicated in the treatment of cervical carcinoma in combination with otherchemotherapeutics or with radiotherapy.

Cisplatin can be used as monotherapy and in combination therapy.

4.2 Posology and method of administration

Adults and Paediatric population

The cisplatin dosage depends on the primary disease, the expected reaction, and on whether cisplatin is used for monotherapy or as a component of combination chemotherapy. The dosage directions are applicable for both adults and children.

For monotherapy, the following two dosage regimens are recommended:

Single dose of 50 to 120 mg/m^2 body surface every 3 to 4 weeks;
15 to 20 mg/m^2/day for five days, every 3 to 4 weeks
If cisplatin is used in combination therapy, the dose of cisplatin must be reduced.
A typicaldose is 20mg/m^2 or more once every 3 to 4 weeks.
For treatment of cervical cancer cisplatin is used in combination with radiotherapy. A

typicaldose is 40 mg/m^2 weekly for 6 weeks.
For warning and precautions to be considered prior to the start of the next treatment cycle.
In patients with renal dysfunction or bone marrow depression, the dose should be reducedadequately
The cisplatin solution for infusion prepared according to instructions should be administeredby intravenous infusion over a period of 6 to 8 hours.
Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realised by intravenous infusion of one of the following solutions:
Sodium chloride solution: 0.9%

Method of administration
Cisplatin 1 mg/ml sterile concentrate is to be diluted before administration. For instructions for dilution of the product before administration.
The diluted solution should be administered only intravenously by infusion.For administration, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided.
Hydration prior to treatment with cisplatin:
Intravenous infusion of 100 to 200ml/Hour for a period of 6 to 12 hours, with a total amount of at least 1 litre.
Hydration after termination of the administration of cisplatin:
Intravenous infusion of another 2 litres at a rate of 100 to 200 ml per hour for a period of 6 to12 hours.
Forced diuresis may be required should the urine secretion be less than 100 to 200 ml/hour after hydration. Forced diuresis may be realised by intravenously administering 37.5g mannitol as a 10% solution (375 ml mannitol solution 10%), or by administration of adiuretic if the kidney functions are normal.
The administration of mannitol or a diuretic is also required when the administrated cisplatin dose is higher than 60 mg/m^2 of body surface.
It is necessary that the patient drinks large quantities of liquids for 24 hours after the cisplatininfusion to ensure adequate urine secretion.

4.3 Contraindications

Hypersensitivity to cisplatin or to any of the excipients listed in section 6.1
Cisplatin may give allergic reactions in some patients. Use is contraindicated in those patients with a history of allergic reaction to cisplatin or other platinum containing compounds, or any component of the formulation. Cisplatin induces nephrotoxicity which is cumulative. It is therefore contraindicated in patients with pre-existing renal impairment.

Cisplatin has also been shown to be cumulatively neurotoxic (in particular ototoxic) and should not be given to patients with pre-existing hearing impairment. Cisplatin is also contraindicated in myelosuppressed patients and those who are dehydrated.

Patients receiving cisplatin should not breast feed.

Concurrent administration of yellow fever vaccine is contraindicated.

4.4 Special warnings and precautions for use

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.
Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing IV sets, needles, catheters and syringes should be avoided.
The solution for infusion should not be mixed with other drugs or additives.
Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

1. Nephrotoxicity

Cisplatin produces severe cumulative nephrotoxicity which may be potentiated by aminoglycoside antibiotics. The serum creatinine, plasma urea or creatinine clearance and magnesium, sodium potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Cisplatin should not be given more frequently than once every 3-4 weeks.
A urine output of 100 ml/hour or greater will tend to minimise cisplatin nephrotoxicity. This can be accomplished by prehydration with 2 litres of an appropriate intravenous solution,and similar post cisplatin hydration (recommended 2,500 ml/m^2/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g., mannitol).

2. Neuropathies

Severe cases of neuropathies have been reported.
These neuropathies may be irreversible and may manifest by paresthesia, areflexia and a proprioceptive loss and a loss of vibration perception. A loss of motor function has also been reported. A neurological examination must be carried out at regular intervals.
Neurotoxicity appears to be cumulative. Prior to each course, the absence of symptoms of peripheral neuropathy should be established.

3. 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 (4000 to 8000 Hz). Decreased ability to hear conversational tones may occur occasionally. Ototoxic effect may be more pronounced in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however, deafness after initial dose of cisplatin has been reported rarely. Ototoxicity may be enhanced with prior simultaneous cranial irradiation and may be related to peak plasma concentration of cisplatin. It is unclear whether cisplatin induced ototoxicity is reversible. Careful monitoring by audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin. Vestibular toxicity has also been reported.

4. Allergic phenomena

Anaphylactic-like reactions to cisplatin have been reported. These reactions have

occurred within minutes of administration to patients with prior exposure to cisplatin and have been alleviated by administration of adrenaline, steroids and antihistamines.
As with other platinum-based products, hypersensitivity reactions appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds.
5. Hepatic function and haematological formula
The haematological formula and hepatic function must be monitored at regular intervals.
6. Carcinogenic potential
In humans, in rare cases the appearance of acute leukaemia has coincided with the use of cisplatin, which was in general associated with other leukaemogenic agent.
Cisplatin is a bacterial mutagen and causes chromosome aberrations in cultures on animal cells. Carcinogenicity is possible but has not been demonstrated. Cisplatin is teratogenic andembryo toxic in mice.
7. Injection site reactions
Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasationreactions is unknown at this time.
WARNINGS
This cytostatic agent had a more marked toxicity than is usually found in antineoplasticchemotherapy.
Renal toxicity, which is above all cumulative, is severe and requires particular precautionsduring administration.
Nausea and vomiting may be intense and require adequate antiemetic treatment.
Close supervision must also be carried out with regard to ototoxicity, myelodepression andanaphylactic reactions.
Preparation of the intravenous solution
Warning
As with all other potentially toxic products, precautions are essential when handling the cisplatin solution. Skin lesions are possible in the event of accidental exposure to the product. It is advisable to wear gloves. In the event the cisplatin solution comes into contactwith the skin or mucous membranes, wash the skin or mucous membranes vigorously with soap and water.
Conforming to the procedures appropriate for the manipulation and elimination of cytostatic agents is recommended.
Before administering the solution to the patient, verify the clarity of the solution and the absence of particles

The vial stopper contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
This medicinal product contains 9 mg sodium per ml dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other FPP's and other forms of Interaction Nephrotoxic

substances:
Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin on the kidneys. During or after treatment with cisplatin caution is advised with predominantly renal eliminated substances, e.g. cytostatic agents such as bleomycin and methotrexate, because of potentially reduced renal elimination.
The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients whohave 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 substances:
Concomitant administration of ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function. Except for patients receiving doses of cisplatin exceeding 60 mg/m^2, whose urine secretion is less than 1000 ml per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.
Oral anticoagulants:
In the event of simultaneous use of oral anticoagulants, it is advisable to regularly check the INR.
Antihistamines, Phenothiazines and others:
Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozone, phenothiazines, thioxanthenes or trimethobenzamines may mask ototoxicity symptoms(such as dizziness and tinnitus).
Anticonvulsive substances:
Serum concentrations of anticonvulsive medicines may remain at subtherapeutic levels during treatment with cisplatin.
Pyroxidine + altretamine combination:
During a randomised study of the treatment of advanced ovarian cancer, the response time was unfavourably affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.
Paclitaxel:
Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance ofpaclitaxel by 33% and therefore can intensify neurotoxicity.
Anti-epileptics:
In patients receiving cisplatin and phenytoin, the serum level of phenytoin might be reduced. This is probably due to reduced absorption and/or increased metabolism. In these patients, one should monitor the levels of phenytoin in plasma, and adjust the dose accordingly.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Cisplatin may be toxic to the foetus when administered to a pregnant woman. Cisplatin should not be used during pregnancy unless the clinician considers the risk in an individual patient to be clinically justified.
During treatment with cisplatin and for a minimum of the following 6 months,

appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

Fertility

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

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.

Breast-feeding

Cisplatin is excreted in breast milk. Patients treated with cisplatin must not breast feed.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Nevertheless, the profile of undesirable effects (like nephrotoxicity) may influence the ability to drive vehicles and use machinery.

4.8 Undesirable effect

The most frequently reported adverse events (>10%) of cisplatin were haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure,nephrotoxicity, hyperuricemia) and fever.

Serious toxic effects on the kidneys, bone marrow and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose- related and cumulative. Ototoxicity may be more severe in children

Frequencies are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000), not known (cannot be estimated from the available data).

Table of Adverse Drug Events Reported During Clinical or Postmarketing Experience(MedDRA terms)

System Organ Class	Frequency	MedDRA term
Infections and infestations	Common	Sepsis
	Not known	Infection
Blood and lymphatic systemdisorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia, thrombotic

		microangiopathy (haemolytic uraemic syndrome)
Neoplasm benign, malignant,and unspecified	Rare	Acute leukaemia
Immune system disorders	Uncommon	Anaphylactoid reaction
Endocrine disorders	Not known	Blood amylase increased, inappropriateantidiuretic hormone secretion
Metabolism and nutritiondisorders	Very common	Hyponatraemia
	Uncommon	Hypomagnesaemia
	Not known	Dehydration, hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalaemia, tetany
Nervous system disorders	Rare	Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
	Not known	Cerebrovascular accident, haemorrhagic stroke,ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
Eye disorders	Not known	Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilledema, retinal pigmentation
Ear and labyrinth disorders	Uncommon	Ototoxicity
	Not known	Tinnitus, deafness
Cardiac disorders	Common	Arrhythmia, bradycardia, tachycardia
	Rare	Myocardial infarction
	Very rare	Cardiac arrest
	Not known	Cardiac disorder
Vascular disorders	Common	Venous thromboembolism
	Not known	Raynaud's phenomenon
Gastrointestinal disorders	Rare	Stomatitis
	Not known	Vomiting, nausea, anorexia, hiccups, diarrhoea

Hepatobiliary disorders	Not known	Hepatic enzymes increased, blood bilirubinincreased
Respiratory, thoracic andmediastinal disorders	Not known	Pulmonary embolism
Skin and subcutaneous tissuedisorders	Not known	Rash, alopecia
Musculoskeletal, connectivetissue and bone disorders	Not known	Muscle spasms
Renal and urinary disorders	Not known	Renal failure acute, renal failure, renal tubular
		disorder
Reproductive system andbreast disorders	Uncommon	Abnormal spermatogenesis
General disorders and administration site condition	Not known	Pyrexia (very common), asthenia, malaise,injection site extravasation

a: Infectious complications have led to death in some patients.

b: Symptoms reported for anaphylactoid reaction such as facial edema (PT-face oedema), wheezing, bronchospasm, tachycardia and hypotension will be included in the parentheses for anaphyactoid reaction in the AE frequency table.

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

d: Local soft tissue toxicity including cellulitis, fibrosis, and necrosis (common) pain (common), oedema (common) and erythema (common) as the result of extravasation.

4.9 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 in the event of an overdose consists of general support measures.

5. Pharmacological Characteristics

5.1 Pharmacodynamic properties

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

Cisplatin has biochemical properties similar to those of bifunctional alkylating agents. The drug inhibits DNA synthesis by producing intrastrand and interstrand

cross links in DNA. Protein and RNA synthesis are also inhibited to a lesser extent.

Although the principal mechanism of action of cisplatin appears to be inhibition of DNA synthesis, other mechanisms, including enhancement of tumour immunogenicity, may be involved in its antineoplastic activity. Cisplatin also has immunosuppressive, radio- sensitising, and antimicrobial properties.

Cisplatin does not appear to be cell cycle specific.

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 detectedin 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.

5.3 Preclinical safety data

Cisplatin has been shown to be mutagenic. It may also have an anti-fertility effect. Other anti-neoplastic substances have been shown to be carcinogenic and this possibility should be borne in mind in long term use of cisplatin.

6. Pharmaceutical Particulars

6.1 List of excipients

Mannitol, Sodium Chloride, Hydrochloric Acid and Water for Injections

6.2 Incompatibilities

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

24 months

6.4 Special precautions for storage

Store below 30°C. Protected from light. Do not Refrigerate.

6.5 Nature and contents of container

50 ml Amber moulded glass vial closed with 20 mm rubber plugs and sealed with20mm flip off Aluminium Seal is placed in a carton along with pack insert.

6.6 Special precautions for disposal

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

7. Marketing Authorization Holder and manufacturing site address:

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-263145,
Uttarakhand, INDIA.

8. Marketing Authorization number:

TAN 21 HM 0259

9. Date of first registration

03 June, 2021

10. Date of revision of the text

April, 2022