Summary of Product Characteristics for

CYTOTIN 50
Cisplatin Injection BP 1mg/ml

1. Name of the medicinal product
Cisplatin Injection BP

2. Qualitative and quantitative composition
Each ml contains:
Cisplatin BP …….. 1mg
Excipients BP ….. q.s.

3. Pharmaceutical form
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 other chemotherapeutics or with radiotherapy.

Cisplatin can be used as monotherapy and in combination therapy.

4.2 Posology and method of administration

Adults and children:

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 typical dose 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 typical dose is 40 mg/m^2 weekly for 6 weeks.

In patients with renal dysfunction or bone marrow depression, the dose should be reduced adequately.

The cisplatin solution for infusion prepared according to instructions should be administered by 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 released 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 to 12 hours.

Forced diuresis may be required should the urine secretion be less than 100 to 200 ml/hour after hydration. Forced diuresis may be released by intravenously administering 37.5g mannitol as a 10% solution (375 ml mannitol solution 10%), or by administration of a diuretic 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 cisplatin infusion to ensure adequate urine secretion.

4.3 Contraindications

Hypersensitivity to cisplatin or to any of the products excipients.

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. Cases of delayed-onset hearing loss have been reported in the paediatric population. Long term follow-up in this population is recommended. 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 has been shown to be teratogenic, embryotoxic and carcinogenic in mice and rats.

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 extravasation reactions is unknown at this time.

<u>WARNINGS</u>
This cytostatic agent had a more marked toxicity than is usually found in antineoplastic chemotherapy.
Renal toxicity, which is above all cumulative, is severe and requires particular precautions during administration.
Nausea and vomiting may be intense and require adequate antiemetic treatment.
Close supervision must also be carried out with regard to ototoxicity, myelodepression and anaphylactic 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 contact with 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

Excipient Information

Cisplatin 10 mg/10 ml (1 mg/ ml) concentrate for solution for infusion contains 35.4 mg of sodium in each 10 ml vial, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Cisplatin 50 mg/50 ml (1 mg/ ml) concentrate for solution for infusion contains 177 mg of sodium in each 50 ml vial, equivalent to 8.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Cisplatin 100 mg/ 100 ml (1 mg/ ml) concentrate for solution for infusion contains 354 mg of sodium in each 100 ml vial, equivalent to 17.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cisplatin may be further prepared for administration with sodium-containing solutions and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products 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 who have previously been given cisplatin.

Renally excreted drugs:

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/m2, 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.

Ifosfamide may increase hearing loss due to cisplatin.

Weakened live vaccines:

Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease. In view of the risk of generalized illness, it is advisable to use an inactive vaccine if available.

Oral anticoagulants:

In the event of simultaneous use of oral anticoagulants such as coumarins/warfarin, 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).

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 of paclitaxel by 33% and therefore can intensify neurotoxicity.

Anti-convulsant agents:

In patients receiving cisplatin and anticonvulsants, plasma levels of anticonvulsant agents (e.g. phenytoin) may be decreased and potentially become subtherapeutic. This is possibly as a result of decreased absorption and/or increased metabolism. In these patients, serum levels of anticonvulsants should be monitored and dosage adjustments made a necessary.

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 29 weeks (at least 7 months) 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 17 weeks (at least 4 months) after the last dose.

Pregnancy

Cisplatin may be toxic to the foetus when administered to a pregnant woman.

Cisplatin has been shown to be teratogenic, embryotoxic and carcinogenic in mice and rats.

Cisplatin should not be used during pregnancy unless the clinician considers the risk in an individual patient to be clinically justified.

Breast-feeding

Limited data from published literature report presence of cisplatin in human milk. Women should not breast-feed while undergoing treatment with cisplatin and for 4 weeks after the last dose of cisplatin.

Fertility

Female

Based on non-clinical 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.

Male

Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported. Although the impairment of spermatogenesis can be reversible, males undergoing cisplatin treatment should be warned about the possible adverse effects on male fertility. Both men and women should seek advice on fertility preservation before treatment.

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 effects

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, hyperuricaemia) 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, < 1/10), uncommon (≥1/1000, < 1/100), rare (≥ 1/10000, < 1/1000), very rare (< 1/10000), and not known (cannot be estimated from the available data).

Table of Adverse Drug Events reported during clinical or post-marketing experience

System Organ Class	Frequency	MedDRA Term
Infections and infestations	Common	Sepsis
	Not known	Infection[a]
Neoplasm benign, malignant, and unspecified	Rare	Acute leukaemia
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anemia
	Not known	Coombs positive haemolytic anaemia, thrombotic microangiopathy (haemolytic uraemic syndrome)

Immune system disorders	Uncommon	Anaphylactoid[b] reactions
Endocrine disorders	Not known	Blood amylase increased, inappropriate antidiurectic hormone secretion
Metabolism and nutrition disorders	Very common	Hyponatremia
	Uncommon	Hypomagnesemia
	Not known	Dehydration, hypokalemia, hypophosphatemia, hyperuricemia, hypocalcemia, tetany
Nervous system disorders	Rare	Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
	Not known	Cerebrovascular accident, hemorrhagic stroke, ischemic stroke, ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
Eye disorders	Not known	Vision blurred, color 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	Thrombotic microangiopathy (hemolytic uremic syndrome), Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism
Gastrointestinal disorders	Rare	Stomatitis
	Not known	Vomiting, nausea, anorexia, hiccups, diarrhea
Hepatobiliary disorders	Not known	Hepatic enzymes increased, blood bilirubin increased
Skin and subcutaneous tissue disorders	Not known	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Not known	Muscle spasms
Renal and urinary disorders	Not known	Renal failure acute, renal failure[c], renal tubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis
General disorders and	Very common	Pyrexia

administration site conditions	Not known	Asthenia, malaise, injection site extravasation[d]

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 anaphylactoid reaction in the AE frequency table.
c: Elevations in BUN and creatinine, serum uric acid, and/or a decrease in creatinine clearance are subsumed under renal insufficiency/failure.
d: Local soft tissue toxicity including tissue cellulitis, fibrosis, and necrosis (common) pain (common), oedema (common) and erythema (common) as the result of extravasation.

4.9 Overdose

Caution is essential in order to prevent an inadvertent overdose.

An acute overdose of cisplatin may result in ocular toxicity (including detachment of the retina), liver failure, deafness, significant myelosuppression, renal failure, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal.

There is no specific antidote in the event of a cisplatin overdose. Even if hemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body due to a strong and rapid fixation of cisplatin to proteins.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Cisplatin has biochemical properties similar to those of bi-functional 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 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.

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.
Cisplatin is embryotoxic in mice and rats, and in both species, deformities have been reported.
Studies in rodents have shown that exposure during pregnancy can cause tumors in adult offspring.
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

Sodium chloride BP
Mannitol BP
Hydrochloric acid BP
Water for injection BP

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

Solution for infusion after dilution:

Chemical and physical in-use stability has been demonstrated for *48 hours at* 2 to *8°C* when protected from light for solutions with a final cisplatin concentration of 0.1 mg/ml after dilution of the cisplatin 1mg/ml concentrate with one of the following solutions:

- Sodium chloride solution 0.9%;

- Mixture of sodium chloride solution 0.9% and glucose solution 5% (1:1);

- Mixture of sodium chloride solution 0.9% and mannitol solution 5% (1:1).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution (etc.) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C. Protect from light. Do not refrigerate.

6.5 Nature and contents of container

Cisplatin Injection BP is available in a vial containing Cisplatin 1 mg/ml.

6.6 Special precautions for disposal and other handling

Single use only. Discard any unused contents.

Dilution

Cisplatin should be diluted in 2 litres of 0.9% sodium chloride injection.

Administration

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Preparation

1. Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.
2. Operations such as reconstitution, dilution and transfer to syringes should be carried out only in the designated area.
3. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.
4. Pregnant personnel are advised not to handle chemotherapeutic agents

Contamination

a) In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.
b) 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.

Disposal

Syringes, container, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

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

7. Marketing authorisation holder
To be allotted

8. Marketing authorisation number(s)
To be allotted

9. Date of first authorisation/renewal of the authorisation
To be allotted

10. Date of revision of the text
20-Nov-23