Summary of Product Characteristics

1. Name of the medicinal product
Cisplatin 50 mg/50 mL Injection

2. Qualitative and quantitative composition

Each ml contains Cisplatin BP 1mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Solution for infusion
A Clear colourless to pale yellow solution

4. Clinical particulars

4.1 Therapeutic indications
Cisplatin is indicated for monotherapy or as part of an existing chemotherapy for advanced or metastatictumours:

- Testicular carcinoma (palliative and curative poly-chemotherapy)
- Ovary carcinoma (stages III and IV)
- Head and neck squamous-cell epithelioma (palliative therapy)

- The treatment of small cell lung carcinoma.
- The treatment of advanced non-small cell lung carcinoma.

4.2 Posology and method of administration
Adults and children:
Dosage of cisplatin depends upon the primary disease, expected reaction, and on whether cisplatin is used as a component of a combination chemotherapy or monotherapy. The current medical literature should be consulted for recommendations on the dosage applicable, based on the diagnosis and the clinical condition.
The following two dosage regimens are recommended, for *Monotherapy*:
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.
In *combination chemotherapy*, the dose of cisplatin must be reduced. A typical dose is 20 mg/m^2 or more once every 3 to 4 weeks unless in the combination therapy of small-cell and non-small-cell lung carcinoma, in which a typical dose of 80 mg/m^2 is administered.

Warnings and precautions to be considered prior to the start of the next treatment cycle.
Patients with bone marrow depression or renal dysfunction, the dose should be reduced adequately.

Method of administration
Cisplatin 1mg/ml concentrate for solution for infusion is to be diluted before use.
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.
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 hoursafter 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%;

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

Hydration prior to treatment with cisplatin:
Intravenous infusion of 100 to 200ml/hour for a period of 6 to 12 hours.

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 realised 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 toensure adequate urine secretion.

4.3 Contraindications
Cisplatin is contraindicated in patients:
- with hypersensitivity to the active substance or other platinum containing compounds or to any of the excipients listed.
- with myelosuppression.
- In dehydrated condition (pre- and post-hydration is required to prevent serious renal dysfunction)
- who are receiving yellow fever vaccine and phenytoin in prophylactic use.
- with pre-existing renal impairment or hearing impairment due to the fact that cisplatin is nephrotoxic and neurotoxic (in particular ototoxic). These toxicities may be cumulative if disorders of this type pre-exist
- Pregnant or breastfeeding.

4.4 Special warnings and precautions for use
Cisplatin reacts with metallic aluminum to form a black precipitate of platinum. All aluminum containing IV sets, catheters, syringes and needles should be avoided.
Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.
Cisplatin must be administered under close supervision by a qualified doctor specialized in the use of chemotherapeutic agents.

Injection site reactions
During the administration of cisplatin, reactions at injection site may occur. 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.

Allergic phenomena
Hypersensitivity reactions appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment, this mostly occurs in all platinum-based products. Cross reactions which may result, is sometimes fatal, have been reported with all the platinum compounds.

Hepatic function and hematological formula
Hepatic function and hematological formula should be monitored at regular intervals.

Nephrotoxicity
As cisplatin causes severe cumulative nephrotoxicity, a urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by pre-hydration with 2 liters 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).

Neuropathies
These neuropathies may be irreversible and may manifest by paraesthesia, areflexia and a proprioceptive loss and

a sensation of vibrations. A loss of motor function has also been reported. A neurologic examination must be carried out at regular intervals. Severe cases of neuropathies have been reported.

Ototoxicity
Ototoxicity has been observed. Decreased ability to hear conversational tones may occur occasionally. In children receiving cisplatin, ototoxic effect may be more pronounced. 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.

Carcinogenic potential
In humans, in rare cases the appearance of acute leukemia has noticed with use of cisplatin, which was in general associated with other leukemogenic agents.
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 and embryotoxic in mice.

Warning
This cytostatic agent has 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.
Warning
Preparation of the intravenous solution
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. Administering the solution to the patient, verify the clarity of the solution and the absence of particles.

This medicinal product contains 35 mg sodium per 10ml vial, equivalent to 1.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction
Attenuated live vaccines
Due to risk of fatal systemic vaccinal disease, yellow fever vaccine is strictly contraindicated.
It is advisable to use an inactivated vaccine if available, in view of the risk of generalized illness.

Paclitaxel
Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity.

Nephrotoxic substances
The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients who have previously been given cisplatin.
Co-administration of nephrotoxic (e.g. aminoglycosides, amphotericin B, cephalosporin, 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 renally eliminated substances, e.g. cytostatic agents such as bleomycin and methotrexate, because of potentially reduced renal elimination.
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.

Oral anticoagulants
It is advisable regularly to check the INR, in the event of simultaneous use of oral anticoagulants

Ototoxic substances
Ifosfamide may increase hearing loss due to cisplatin.
Co-administration of ototoxic (e.g. loop diuretics, aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin on auditory function. Except for patients receiving doses of cisplatin exceeding 60mg/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.

Anticonvulsive substances
During treatment with cisplatin, serum concentrations of anticonvulsive medicines may remain at sub-therapeutic levels.

Pyridoxine + altretamine combination
The response time was unfavorably affected when pyridoxine in combination with altretamine (hexamethylmelamine) and cisplatin during a randomized study of the treatment of advanced ovarian cancer.

Antihistamines, Phenothiazines and others
Simultaneous use of antihistamines, phenothiazines, meclozine, buclizine, cyclizine, loxapine, thioxanthenes or trimethobenzamides may mask ototoxicity symptoms (such as tinnitus and dizziness).

4.6 Fertility, pregnancy and lactation
Pregnancy
There is no sufficient data from the use of cisplatin in pregnant women, but based on its pharmacologicalproperties 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
Breastfeeding during the therapy is contraindicated because cisplatin is excreted in human milk.

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
Patients who suffer from these effects (e.g. feeling sleepy or vomiting) must avoid driving and operatingmachinery because cisplatin has minor or moderate influence on the ability to drive and use machines.

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.
The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories:
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	Uncommon	Acute leukemia
Blood and lymphatic systemdisorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anemia
	Not known	Coombs positive hemolytic anemia
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], renaltubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis
General disorders and administration site conditions	Very common	Pyrexia
	Not known	Asthenia, malaise, injection siteextravasation[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, andhypotension 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

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 hoursafter 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Cisplatin is an organic 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 Pharmacokinetic properties

Distribution

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

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

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.

Chronic toxicity:

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

Reproductive toxicity:

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.

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

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride BP
Mannitol BP
Hydrochloric acid, dilute BPWater
for injection BP

6.2 Incompatibilities

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

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 except those mentioned above.

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 as stated in Special precautions for handling.

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.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Cisplatin Injection was developed in concentration of 1mg/ml supplied in 10mg/10 ml:

10ml Amber color Vial which contains Cisplatin 10mg

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 in Posology and method for administration 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 pale yellow, 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 is 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 notwork with cisplatin.
Skin contact: Rinse with large quantities of water. Apply an ointment if you have a temporary burningfeeling. (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 plasticbag and seal it. In the case of spillage all items coming into contact with cisplatin should be handled anddisposed in accordance to local cytotoxic guidelines.
Any unused product or waste material should be disposed of in accordance with localrequirements.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

TAN 21 HM 0207

9. Date of first authorisation/renewal of the authorisation

Date of first authorization: June 03, 2021
Date of latest renewal: N/A

10. Date of revision of the text

April, 2022