Summary of Product Characteristics

1. ***Name of the medicinal product:***

a) ***Product Name:*** PLATICIN-10mg

b) ***Strength*****:** 10mg/10ml

c) ***Pharmaceutical Dosage Form*****:** Liquid Injection

2. ***Qualitative and quantitative composition***

Each ml contains

Cisplatin BP	1 mg
Sodium Chloride USP	9 mg
Hydrochloric Acid USP (To adjust pH)	q.s
Water for Injection USP	q.s

Contains No Antimicrobial Preservatives

3. **Pharmaceutical form**: Liquid Injection

4. **Clinical particulars**

A. **Therapeutic indications**

CISPLATIN is indicated as therapy for:

Metastatic testicular tumors

In established combination therapy with other approved chemotherapeutic agents in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Metastatic ovarian tumors

In established combination therapy with other approved chemotherapeutic agents in patients who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of cisplatin and cyclophosphamide. CISPLATIN, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received cisplatin therapy.

Advanced bladder cancer

As a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy

B. ***Posology and method of administration***

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

The usual CISPLATIN dose for the treatment of ***testicular cancer*** in combination with other approved chemotherapeutic agents is 20 mg/m^2 I.V daily for 5 days per cycle.
The usual CISPLATIN dose for the treatment of ***metastatic ovarian tumors*** in combination with cyclophosphamide is 75-100 mg/m^2 I.V per cycle once every four weeks (day 1).

The dose of cyclophosphamide when used in combination with cisplatin is 600 mg/m^2 I.V once every four weeks (day 1). In combination therapy, CISPLATIN and cyclophosphamide are administered sequentially but as a single agent, CISPLATIN should be administered at a dose of 100 mg/m^2 I.V per cycle once every four weeks.

In patients with ***advanced bladder cancer*** CISPLATIN should be administered as a single agent at 50-70 mg/m^2 I.V per cycle once every 3-4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy.

For heavily pretreated patients an initial dose of 50 mg/m2 per cycle repeated every four weeks is recommended.

It is recommended that all patients are to undergo pretreatment hydration with 1-2 liters of fluid infused for 8-12 hours prior to cisplatin dose. CISPLATIN is then required to be diluted in 2 liters of 5 % dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol and infused over a 6-8 hour period. If the diluted solution is not used within 6 hours protect the solution from light. It is not advisable to dilute cisplatin in just 5 % dextrose injection. Adequate hydration and urinary output must be maintained during the following 24 hours after treatment. The course of cisplatin should not be repeated until serum creatinine is below 1.5 mg/100 ml and/or the BUN is below 25 mg/100 ml. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets $\geq$ 100,000/mm^3, WBC $\geq$ 4,000/mm^3). Subsequent doses of

CISPLATIN should not be given until an audiometric analysis indicates that auditory acuity is within normal limits. As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If CISPLATIN contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

The aqueous solution should be used intravenously only and should be administered by I.V infusion over a 6-8 hour period.
Note: Exercise caution to prevent inadvertent CISPLATIN overdosage. It is advisable to call the prescriber if dose is greater than 100 mg/m^2 per cycle.

Additionally the aluminum cap and flip-off seal of vial may be imprinted with the following statement: ***Call Dr. if the dose is > than 100 mg/m^2/cycle.***

C. Contraindications

Cisplatin is contraindicated in patients

- with hypersensitivity to cisplatin or other platinum compounds or to any of the excipients;
- with renal dysfunction (creatinine clearance < 60 ml/min);
- in dehydrated condition (pre- and post-hydration is required to prevent
- serious renal dysfunction);
- with myelosuppression;
- with a hearing impairment;
- with neuropathy caused by cisplatin
- in combination with live vaccines, including yellow fever vaccine
- in combination with phenytoin in prophylactic use

Pregnancy

There is insufficient data about the use of cisplatin in pregnant women. However, based on the pharmacological properties, cisplatin is suspected to cause serious birth defects. Animal studies have shown reproductive toxicity and transplacental carcinogenity

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

Cisplatin should not be used during pregnancy unless clearly necessary.

During treatment with Cisplatin Pharmachemie and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

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

A preconceptual consult is recommended when patients wish to have children after treatment with cisplatin.

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 treatment.

Lactation

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

D. Special warnings and precautions for use

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

There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of Cisplatin injection or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. Elderly patients may be more susceptible to peripheral neuropathy. Loss of motor function has also been reported. Anaphylactic-like reactions to Cisplatin injection have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to Cisplatin injection, and have been alleviated by administration of epinephrine, corticosteroids, and antihistamines. Cisplatin injection can commonly cause ototoxicity which is cumulative and may be severe. Audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug. Certain genetic variants in the thiopurine S-methyltransferase (TPMT) gene are associated with increased risk of ototoxicity in children administered conventional doses of cisplatin. Children who do not have one of these TPMT gene variants remain at risk for ototoxicity. All pediatric patients receiving cisplatin should have audiometric testing at baseline, prior to each subsequent dose, of drug and for several years post therapy. Cisplatin injection can cause fetal harm when administered to a pregnant woman. Cisplatin injection is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice Cisplatin injection is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant. The carcinogenic effect of Cisplatin injection was studied in BD IX rats. Cisplatin injection was administered intraperitoneally (i.p.) to 50 BD IX rats for 3 weeks, 3 X 1 mg/kg body weight per week. Four hundred and fifty-five days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma. The development of acute leukemia coincident with the use of Cisplatin injection has been reported. In these reports, Cisplatin injection was generally given in combination with other leukemogenic agents. Injection site reactions may occur during the administration of Cisplatin injection. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Precautions: Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly. Drug Interactions Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and Cisplatin injection

E. Interaction with other medicinal products and other forms of interaction

Common to all Cytotoxic:

Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) 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.

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.

Contraindicated ones

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

Use of living virus vaccinations is not recommended given within three months following the end of the cisplatin treatment.

Serum concentrations of anticonvulsive medicines may remain at subtherapeutic levels during treatment with cisplatin.

Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control when phenytoin is given as current treatment. During cisplatin therapy starting a new anticonvulsivant treatment with phenytoin is strictly contraindicated.

Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity.
Simultaneous use of myelosuppressives or radiation will boost the effects of cisplatin’s myelosuppressive activity.

Cisplatin given in combination with bleomycin and vinblastin can lead to a Raynaudphenomenon.

In a study of cancer patients with metastatic or advanced tumors, docetaxel in combination with cisplatin induced more severe neurotoxic effects (dose-related and sensoric) than either drug as a single agent in similar doses.

Prohibited ones

The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients who have previously been given cisplatin.

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.

Simultaneous use of ifosphamide causes increased protein excretion.

Ifosfamide may increase hearing loss due to cisplatin.

Requiring precautionary measures

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.

The occurrence of nephrotoxicity caused by cisplatin may be intensified by concomitant treatment with antihypertensives containing furosemide, hydralazine, diazoxide, and propranolol.

It may be required to adjust the dosage of allopurinol, colchicine, probenecid, or sulfinpyrazone if used together with cisplatin, since cisplatin causes an increase in serum uric acid concentration.

In the event of simultaneous use of oral anticoagulants, it is advisable regularly to check the INR.

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

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 Pharmachemie.

Chelating agents like penicillamine may diminish the effectiveness of cisplatin.

In concomitant use of cisplatin and ciclosporin the excessive immunosuppression with risk of lymphoproliferation is to be taken into consideration.

F. Pregnancy and lactation

Pregnancy

There is insufficient data about the use of cisplatin in pregnant women. However, based on the pharmacological properties, cisplatin is suspected to cause serious birth defects. Animal studies have shown reproductive toxicity and transplacental carcinogenity.

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

Cisplatin should not be used during pregnancy unless clearly necessary.

During treatment with Cisplatin Pharmachemie and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both sexes.

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

A preconceptual consult is recommended when patients wish to have children after treatment with cisplatin.

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 treatment.

Lactation

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

G. 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.

H. Undesirable effects

Undesirable effects depend on the used dose and may have cumulative 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 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).

Infections and infestations
Common: Infections. Sepsis.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Rare: Cisplatin increases the risk of secondary leukaemia. The risk of secondary leukaemia is dose-dependent and not age- and sex-related.
Carcinogenicity is theoretically possible (based on cisplatin's mechanism of action).
Blood and lymphatic system disorders
Very common: Dose dependent, cumulative and mostly reversible leukopenia, thrombocytopenia and anaemia are observed in 25-30% of patients treated with cisplatin.

Common: A considerable decrease in the number of white blood cells often occurs approximately 14 days after the use (less than 1.5 × 109/l in 5% of the patients). A decrease of the number of platelets is observed after approximately 21 days (less than 10% of the patients showed a total less than 50 × 109/l) (the recovery period is approximately 39 days). Anaemia (decreases of greater than 2g haemoglobin) occurs at approximately the same frequency, but generally with a later onset than leukopenia and thrombocytopenia.

Rare: Coombs positive haemolytic anaemia was reported and was reversible if the use of cisplatin was terminated. Literature has been published regarding hemolysis possibly caused by cisplatin. Serious bone marrow failure (including agranulocytosis and/or aplastic anaemia) may occur after high doses of cisplatin.

Very rare: Thrombotic microangiopathy combined with haemolytic uraemic syndrome.

Immune system disorders
Uncommon: Hypersensitivity may present as rash, urticaria, erythema, or pruritus allergic.

Rare: oedema and fever have been reported. Treatment with antihistamines, epinephrine (adrenaline) and steroids may be required.

Immunosuppression has been documented.

Endocrine disorders
Very rare: Syndrome of inappropriate antiduretic hormone secretion.

Metabolism and nutrition disorders
Rare: Hypomagnaesaemia, hypocalcaemia, hyponatraemia, hypophosphataemia and hypokalaemia with muscle spasms and/or electrocardiogram changes occur as a result of damage to the kidney caused by cisplatin, thus reducing the tubular resorption of cations. Hypercholesterolemia. Increased blood amylase.

Very rare: Increased blood iron.

Nervous system disorders
Common: Neurotoxicity caused by cisplatin is characterised by peripheral neuropathy (typically bilateral and sensory), and rarely by the loss of taste or tactile function, or by optic retrobulbar neuritis with reduced visual acuity and cerebral dysfunction (confusion, disarthria, individual cases of cortical blindness, loss of memory, paralysis). Lhermitte's sign, autonomous neuropathy and myelopathy of the spinal cord have been reported.

Rare: Cerebral disorders (including acute cerebrovascular complications, cerebral arteritis, occlusion of the carotic artery, and encephalopathy).

Very rare: Seizures.
The use of cisplatin must be terminated immediately if one of the above mentioned cerebral symptoms occurs. Neurotoxicity caused by cisplatin may be reversible. However, the process is irreversible for 30-50% of the patients, even after discontinuation of the treatment. Neurotoxicity may occur after the first dose of cisplatin, or after a long-term therapy. Severe neurotoxicity may occur in patients who have received cisplatin at high concentrations or for a prolonged period.

Eye disorders
Rare: Blindness during a combination treatment with cisplatin. Following high-dose cisplatin application impairment of colour vision and eye movement has been reported.

Very rare: Papilloedema, optic neuritis and cortical blindness have been reported following treatment with cisplatin. One case of unilateral optic neuritis retrobulbar with reduced visual acuity has been reported after combination chemotherapy followed by cisplatin treatment.

Ear and labyrinth disorders
Very common: Hearing impairment has been documented in approximately 31% of patients treated with 50 mg/m^2 cisplatin. The defect is cumulative, may be irreversible, and is sometimes limited to one ear.

Ototoxicity manifests itself as tinnitus and/or hearing impairment at higher frequencies (4,000-8,000 Hz). Hearing impairment at frequencies of 250-2000Hz (normal hearing range) was noticed for 10 to 15% of the patients.

Common: Deafness and vestibular toxicity combined with vertigo may occur. Prior or simultaneous cranial radiation increases the risk of hearing loss.

Rare: Patients may lose the ability to conduct a normal conversation. Cisplatin-induced hearing impairment may be serious for children and elderly patients.

Cardiac disorders
Common: Arrythmia including bradycardia, tachycardia and other electrocardiogram changes e.g. ST-segment changes, signs of myocardial ischemia have been observed particularly in combination with other cytotoxics.

Rare: Hypertension and myocardial infarction may occur, even some years after chemotherapy. Severe coronary artery disease.

Very rare: Cardiac arrest has been reported after treatment with cisplatin combined with other cytotoxics.

Vascular disorders
Common: Phlebitis may occur in the area of the injection after intravenous administration.

Very rare: Vascular disorders (cerebral or myocardial ischaemia, impairment of the peripheral circulation related to the Raynaud's syndrome) were linked to cisplatin chemotherapy.

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, pneumonia and respiratory failure.

Gastrointestinal disorders

Very common: Anorexia, nausea, vomiting and diarrhoea occur between 1 and 4 hours after the use of cisplatin.

Uncommon: Metallic setting on the gums.

Rare: Stomatitis, diarrhoea.

Hepatobiliary disorders

Common: Abnormal hepatic function with increased transaminases and blood bilirubin are reversible.

Rare: Reduced blood albumin levels were noticed and may be linked to the treatment with cisplatin.

Skin and subcutaneous tissue disorders

Common: Erythema and skin ulcer may occur in the area of the injection after intravenous administration.

Uncommon: Alopecia.

Renal and urinary disorders

Very common: Renal failure after single or multiple doses of cisplatin. A mild, reversible renal dysfunction may be observed after a single intermediary dose of cisplatin (20 mg/m^2 to < 50 mg/m^2). The use of a single high dose (50-120 mg/m^2), or repeated daily use of cisplatin, may cause renal failure with tubular renal necrosis presenting as uraemia or anuria. Renal failure may be irreversible. The nephrotoxicity is cumulative and may occur 2-3 days, or two weeks after the first dose of cisplatin. Serum creatinine and urea concentrations may increase. Nephrotoxicity was observed in 28-36% of patients without sufficient hydration after a single dose of 50 mg/m^2 of cisplatin.

Hyperuricaemia occurs asymptomatically or as gout. Hyperuricaemia has been reported in 25-30% of patients in conjunction with nephrotoxicity.

Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin-induced nephrotoxicity.

Reproductive system and breast disorders

Uncommon: Abnormal spermatogenesis and ovulation, and painful gynaecomastia.

General disorders and administration site conditions

Very common: Fever.

Common: Localised oedema and pain may occur in the area of the injection after intravenous administration.

Uncommon: Hiccups, asthenia, malaise.

I. Overdose

Symptoms of overdose involve above mentioned side effects in an excessive manner. Efficient hydration and osmotic diuresis can aid in reduction of toxicity, provided this is applied immediately after overdose.

In case of overdose (≥200 mg/m^2), direct effects on the respiratory centre are possible, which might result in life-threatening respiratory disorders and acid base equilibrium disturbance due to passage of the blood brain barrier

5. Pharmacological properties

A. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents

ATC code: L01XA01

Alkylating agents work by three different mechanisms: 1) attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA, 2) DNA damage via the formation of cross-links (bonds between atoms in the DNA) which prevents DNA from being separated for synthesis or transcription, and 3) the induction of mispairing of the nucleotides leading to mutations

B. Pharmacokinetic properties

After intravenous administration, cisplatin is rapidly distributed among all tissues. Following cisplatin doses of 20 to 120 mg/m², the concentrations of platinum are highest in liver, prostate and kidney, somewhat lower in bladder, muscles, testicle, pancreas and spleen and lowest in bowel, adrenal, heart, lung, cerebrum and cerebellum. 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/m2 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 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.

C. ***Preclinical safety data***

Chronic toxicity:

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

Mutagenity and carcinogenity:

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

Reproductive toxicity:

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

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

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

6. ***Pharmaceutical particulars***

A. ***List of excipients***

Sodium Chloride USP, Hydrochloric acid USP, Water for Injection USP

B. ***Incompatibilities***

Do not bring in contact with aluminium. Cisplatin reacts with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should be avoided. Cisplatin decomposes with solution in media with low chloride content; the chloride concentration should at least be equivalent to 0.45% of sodium chloride.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

C. ***Shelf life:*** 2 years

D. ***Special precautions for storage***

Store at a temperature between 15 to 25 °C (59° to 77 °F). Protect from light. Do not freeze.

E. ***Nature and contents of container:***

10ml amber glass vial stoppered with red coloured bromo butyl rubber stopper and properly sealed with aluminium seal having green coloured flip off.

F. Special precautions for disposal

Instruction of application

Like with all anti-neoplastic products caution is needed with the processing of cisplatin. Must be diluted before use. Dilution should take place under aseptic conditions by trained personnel in an area specifically intended for this. Protective gloves should be worn for this. Precautions should be taken to avoid contact with the skin and mucous membranes. If skin contact did occur anyway, the skin should be washed with soap and water immediately. With skin contact tingling, burns and redness have been observed. In case of contact with the mucous membranes they should be copiously rinsed with water.

After inhalation dyspnoea, pain in the chest, throat irritation and nausea have been reported.

Pregnant women must avoid contact with cytostatic drugs.

Bodily waste matter and vomit should be disposed with care.

If the solution is cloudy or a deposit that does not dissolve is noticed, the bottle should be discarded.

A damaged bottle must be regarded and treated with the same precautions as contaminated waste.

Contaminated waste must be stored in waste containers specifically marked for this. See section "Disposal".

Preparation of the intravenous administration

Take the quantity of the solution that is needed from the bottle and dilute with at least 1 litre of the following solutions:

- sodium chloride 0.9%
- mixture of sodium chloride 0.9% / glucose 5% (1:1), (resulting final concentrations: sodium chloride 0.45%, glucose 2.5%)
- sodium chloride 0.9% and 1.875% mannitol, for injection
- sodium chloride 0.45%, glucose 2.5% and 1.875% mannitol for injection

Always look at the injection before use. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used. Only a clear solution, free from particles should be administered.

DO NOT bring in contact with injection material that contains aluminium

DO NOT administer undiluted

With respect to microbiological, chemical and physical stability with use of the undiluted solutions.

Disposal

All materials that have been used for the preparation and administration, or which have been in contact with cisplatin in any way, must be disposed of according to local cytotoxic guidelines. These measures will help to protect the environment.

7. Manufacturer

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