SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cisplatin 1mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of concentrate for solution for infusion contains 1 mg of cisplatin.

Each single vial of 50 ml concentrate for solution for infusion contains 50 mg of cisplatin.
Each single vial of 100 ml concentrate for solution for infusion contains 100 mg of cisplatin.

Excipient(s) with known effect:
Each ml of solution contains 3.54 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colorless to pale yellow solution in an amber glass vial, which is practically free from particles.

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

Posology

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 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.

For warning and precautions to be considered prior to the start of the next treatment cycle (see section 4.4).

In patients with renal dysfunction or bone marrow depression, the dose should be reduced adequately (see section 4.3).

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%
- 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, with a total amount of at least 1 litre.

Hydration after termination of the treatment with 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 to ensure adequate urine secretion.

Method of administration

Cisplatin is to be diluted before administration and should be administered by intravenous infusion over a period of 6 to 8 hours. For instructions for dilution of the product before administration see section 6. 6.

The diluted solution should be administered only intravenously by infusion (see above). For administration, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided (see section 6.2).

4.3 Contraindications

Cisplatin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or other platinum-containing compounds.
- with pre-existing renal impairment (creatinine clearance < 60 ml/min)*
- in dehydrated condition (pre- and post-hydration is required to prevent serious renal dysfunction).
- with myelosuppression;
- with pre-existing hearing impairment*.
- with neuropathy caused by cisplatin
- who are breastfeeding (see section 4.6)
- in combination with live vaccines, including yellow fever vaccine (see section 4.5).
- in combination with phenytoin in prophylactic use (see section 4.5)

* 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.

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 aluminum containing IV sets, needles, catheters and syringes should be avoided. (see section 6.2.)

The solution for infusion should not be mixed with other drugs or additives. (see section 6.2.)

Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

Before, during and after administration of cisplatin, the following parameters must be determined:

- renal function.
- hepatic function.
- hematopoiesis functions (number of red and white blood cells and blood platelets).
- serum electrolytes (calcium, sodium, potassium, magnesium).

Repeating administration of cisplatin must be delayed until normal values are achieved for the following parameters:

- Serum creatinine < 130 µmol/l rsp. 1.5 mg/dl
- Urea < 25 mg/dl
- White blood cells > 4.000/µl resp. > 4.0 x 10^9/l
- Blood platelets > 100.000/µl resp. > 100 x 10^9/l
- Audiogram: results within the normal range.

<u>Nephrotoxicity</u>

Cisplatin causes severe cumulative nephrotoxicity. 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).

Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin- induced nephrotoxicity.

<u>Neurotoxicity</u>

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.

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. (see section 4.8).

Allergic reactions

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 (see sections 4.3 and 4.8).

Hepatic function and haematological formula

The haematological formula and hepatic function must be monitored at regular intervals.

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 and embryo toxic in mice.

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.

In cases of extravasation:

- immediately end the infusion of cisplatin;
- do not move the needle, aspirate the extravasate from the tissue, and rinse with

sodium chloride solution 0.9% (if solutions with cisplatin concentrations higher than recommended were used; see section 6.6.).

WARNINGS

This cytostatic agent had a more marked toxicity than is usually found in antineoplastic chemotherapy.

The toxicity caused by cisplatin may be amplified by the combined use with other medicinal products, which are toxic for the said organs or systems.

Special care is required for patients with acute bacterial or viral infections.

Nausea and vomiting may be intense and require adequate antiemetic treatment.

Nausea, vomiting and diarrhoea often occur after administration of cisplatin (see section 4.8). These symptoms disappear in most patients after 24 hours. Less serious nausea and anorexia may continue up to seven days after the treatment.

Prophylactic administration of an anti-emetic may be effective in alleviating or preventing nausea and vomiting. The liquid loss caused by vomiting and diarrhoea must be compensated.

Close supervision must also be carried out with regard to ototoxicity, myelodepression and anaphylactic reactions (see section 4.8).

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.

Contraception

Male and female patients should use effective contraception during and for at least 6 months after the treatment with cisplatin (see section 4.6).

Important information about some of the ingredients of Cisplatin

Cisplatin 50mg/50ml contains 177 mg sodium per vial, equivalent to 8.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cisplatin 100mg/100ml contains 354 mg sodium per vial, equivalent to 17.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

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.

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.

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.

Simultaneous use of ifosphamide causes increased protein excretion.

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 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.

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 (see section 4.3). 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.

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).

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.

Anticonvulsive substances:

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 (see section 4.3.).

Other

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 Raynaud-phenomenon

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.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Women of childbearing potential and male patients have to use effective contraception during and up to 6 months after treatment.

Pregnancy

There is insufficient data about the use of cisplatin in pregnant women. However, based on the pharmacological properties, cisplatin is suspected to be toxic to the foetus Animal studies have shown reproductive toxicity and transplacental carcinogenity (see section 5.3). Cisplatin should not be used during pregnancy unless clearly necessary

Breast-feeding

Cisplatin is excreted in breast milk. Breast feeding is contra-indicated during treatment with cisplatin.

Fertility

Genetic consultation is recommended if the patient wishes to have children after ending treatment. Cisplatin can cause temporary or permanent infertility. Sperm cryopreservation can be considered (see also section 4.4).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, the profiles of undesirable effects (central nervous system and special senses) may lead to minor or moderate influence on the ability to drive and use machines. Patients who suffer from these effects (e.g. sleepy or vomiting) must avoid driving and operating machinery.

4.8 Undesirable effects

Undesirable effects depend on the dose administered and may be cumulative.

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[a]
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia
Neoplasm benign, malignant, and unspecified	Rare	Acute leukaemia
Immune system disorders	Uncommon	Anaphylactoid[b] reaction Hypersensitivity
	Rare	Immunosuppression
Endocrine disorders	Not known	Blood amylase increased, inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Very common	Hyponatraemia
	Uncommon	Hypomagnesaemia
	Rare	Hypercholesterolemia
	Not known	Dehydration, hypokalaemia, hypophosphatemia, hypocalcaemia, tetany
Nervous system disorders	Common	Neurotoxicity
	Rare	Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
	Not known	Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke, ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic Neuropathy; hyperuricaemia
Eye disorders	Rare	Optic retrobulbar neuritis Impaired eye movement
	Very rare	Increased blood iron
	Not known	Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilledema, retinal pigmentation
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Ototoxicity
	Not known	Tinnitus, deafness
Cardiac disorders	Common	Arrhythmia, bradycardia, tachycardia
	Rare	Myocardial infarction, severe coronary artery disease
	Very rare	Cardiac arrest
	Not Known	Cardiac disorder

Vascular disorders	Common	Phlebitis at injection site Venous thromboembolism
	Rare	Hypertension
	Not Known	Thrombotic microangiopathy (haemolytic uremic syndrome), Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, pneumonia, respiratory failure
	Not known	Pulmonary embolism
Gastrointestinal disorders	Rare	Stomatitis
	Not know	Vomiting, nausea,anorexia, hiccups, diarrhoea
Hepatobiliary disorders	Not known	Hepatic enzymes increased, blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	Erythema, skin ulcer, localised oedema
	Uncommon	Pruritis, urticaria
	Not known	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Not known	Muscle spasms
Renal and urinary disorders	Very common	Renal failure[c)] acute, renal tubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis and ovulation, and painful gynaecomastia
General disorders and administration site condition	Not known	Pyrexia (very common), asthenia, malaise, injection site extravasation[d]
Investigations	Rare	Blood albumin decreased

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

[b]: Symptoms reported for anaphylactoid reaction such as facial oedema (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 decrease in creatinine clearance are 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Caution is essential in order to prevent an inadvertent overdose

Efficient hydration and osmotic diuresis can aid in reduction of toxicity, provided this is applied immediately after overdose.

In case of overdose (≥200 mg/m2), 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.

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 overdosage 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.

Convulsions may be treated with appropriate anticonvulsants. Renal function, cardiovascular function and blood counts should be monitored daily in order to assess the potential toxicity to these systems. Serum magnesium and calcium levels should be carefully monitored as should symptoms and signs of voluntary muscle irritability. If symptomatic tetany develops, electrolyte supplements should be administered. Serum liver enzymes and uric acid should also be monitored daily after an acute overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Cisplatin is an inorganic compound which contains a heavy metal [cis-diamminedichloridoplatinum(II)]. It inhibitsDNA-synthesis by the formation of DNA cross-links. Protein and RNA synthesis are inhibited to a lesser extent.

Although the most important mechanism of action seems to be inhibition of DNA synthesis, other mechanisms can also contribute to the antineoplastic activity of cisplatin, including the increase of tumour immunogenicity. The oncolytic properties of cisplatin are comparable to the alkylating agents. Cisplatin also has immunosuppressive, radiosensitising, and antibacterial properties. Cisplatin seems to be cell-cycle non-specific. The cytotoxic action of cisplatin is caused by binding to all DNA-bases, with a preference for the N-7 position of guanine and adenosine

5.2 Pharmacokinetic properties

Distribution

After intravenous administration cisplatin quickly distributes across all tissues; cisplatin badly penetrates in the central nervous system. The highest concentrations are reached in the liver, kidneys, bladder, muscle tissue, skin, testes, prostate, pancreas and spleen.

Elimination

After intravenous administration the elimination of filterable, non-protein bound cisplatin runs biphasic, with an initial and terminal half-life of 10-20 minutes and 32-53 minutes, respectively. The elimination of the total quantity of platinum runs triphasic with half-lives of 14 minutes, and 274 minute and 53 days respectively.

Cisplatin is bound to plasma proteins for 90%.

The excretion primarily takes place via the urine: 27-43% of the administered dose is recovered in the urine in the first five days after the treatment. Platinum is also excreted in the bile.

5.3 Preclinical safety data

Chronic toxicity

Chronic toxicity models indicate renal damage, bone marrow depression, gastro-intestinal disorders and ototoxicity.

Mutagenicity en carcinogenity

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

Reproductive toxicity

In mice, gonadal suppression, resulting in amenorrhoea or azoospermia has been observed, which can be irreversible and result in infertility. In female rats cisplatin induced morphological changes in the ovaries, causing partial and reversible infertility.

Studies in rats showed that exposure during pregnancy can cause tumours in adult offspring.

Cisplatin is embryotoxic and teratogenic for mice and rats, and defects have been reported for both species. Cisplatin is excreted in the breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid 37%
Sodium hydroxide
Water for injections

6.2 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.

Cisplatin should only be used with those diluents specified in section 6.6.

6.3 Shelf life

Prior to first use: 3 years.

Shelf life after opening

Chemical and physical stability was demonstrated for 56 days at 20 - 25 °C, exposed or protected from light. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Shelf life after dilution

Chemical and physical in-use stability after dilution with infusion fluids described in section 6.6, indicate that after dilution with recommended intravenous fluids, Cisplatin remains stable for 48 hours at 15 - 25 °C room temperature under protection from light

The diluted solution should be protected from light.

Do not store diluted solutions in the refrigerator or freezer

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and dilution should taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Prior to first use: Do not store above 25°C. Do not refrigerate or freeze. Keep container in the outer carton in order to protect from light.

Preparation of the intravenous administration

Take the quantity of the solution that is needed from the vial and dilute with 1 or 2 liters of the

following solutions:

- sodium chloride 0.9%,

-Misture of sodium chloride 0.9% / glucose 5 (1:1), (resulting final concentration: sodium chloride 0.45%, glucose 2.5%)

- sodium chloride 0.9% and 1.875% mannitol

- sodium chloride 0.45%, glucose 2.5% and 1.875% mannitol

Compatibility with the above solutions has been demonstrated at concentration of 0.1 and 0.22 mg/ml.

DO NOT bring in contact with injection material that contains aluminium

DO NOT administer undiluted

For storage conditions after dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Type 1 amber glass vials of 50 and 100 mL with a Teflon-coated chlorobutyl rubber stopper and sealed with an aluminium flip-off cap Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Single use only. Discard any unused contents. Refer to local cytotoxic handling guidelines.

Dilution:

Cisplatin 1 mg/ml should be diluted in 1 and 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 (Guidelines):

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

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