Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cisplatin 1 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial of 10 ml concentrate for solution for infusion contains 10 mg of cisplatin.
One vial of 20 ml concentrate for solution for infusion contains 20 mg of cisplatin.
One vial of 50 ml concentrate for solution for infusion contains 50 mg of cisplatin.
One vial of 100 ml concentrate for solution for infusion contains 100 mg of cisplatin.

Excipient(s) with known effect:
Each ml of solution contains 0.1 to 0.2 millimoles per ml of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to pale yellow solution.

The pH is between 3.5 to 6.5.

The osmolarity is between 250 to 400 mOsmol/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cisplatin is intended for the treatment of:

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

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

Cisplatin can be used as monotherapy and in combination therapy.

4.2 Posology and method of administration

Posology

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 chemotherapy, the dose of cisplatin must be reduced. A typical dose is 20 mg/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 warnings 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.

The cisplatin solution for infusion prepared according to instructions (see section 6.6.) 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 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).

(1:1)
Hydration prior to treatment with cisplatin:
Intravenous infusion of 100 to 200 ml/hour for a period of 6 to 12 hours, with a total amount of at least 1L.

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/m2 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 1 mg/ml concentrate for solution for infusion is to be diluted before administration. For instructions on dilution of the product before administration, see section 6.6.

The diluted solution should be administered only intravenously by infusion (see below). 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 cisplatin or other platinum compounds or to any of the excipients listed in section 6.1.

- with renal impairment (creatinine clearance < 60 ml/min). Cisplatin is nephrotoxic;

- in dehydrated condition (pre and post hydration is required to prevent serious renal dysfunction);

- with myelosuppression;

- with a hearing impairment. Cisplatin is neurotoxic (in particular ototoxic);

- with neuropathy caused by cisplatin

- who are breast-feeding (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)

- Nephrotoxicity, neurotoxicity and ototoxicity is cumulative, and need to be considered if disorders relevant to these pre-exist.

4.4 Special warnings and precautions for use

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing IV sets, needles, catheters and syringes should be avoided.

Cisplatin must be administered under close supervision by a qualified doctor specialized in the use of chemotherapeutic agents.

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

Blood tests should be done to monitor the following parameters, before and after the administration of cisplatin:
renal function;
hepatic function;
blood counts;
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 or 1.5 mg/dl
- Urea < 25 mg/dl
- White blood cells > 4.000/µlor > 4.0 x 109/l
- Blood platelets > 100.000/µlor > 100 x 109/l
- Audiogram: results within the normal range.

Allergic reactions
As with other platinum-based products, hypersensitivity reactions (anaphylactic- like reactions) appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment (antihistamines, adrenaline and/or glucocorticoids). Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see section 4.8 and section 4.3).

Nephrotoxicity
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 prehydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 ml/m2/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (eg, mannitol). Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin- induced nephrotoxicity.

Neurotoxicity
- Severe cases of neuropathies have been reported.

- These neuropathies may be irreversible and may manifest by paresthesia, 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.
- Special caution must be exercised for patients with peripheral neuropathy not caused by cisplatin.

Ototoxicity
Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m2, 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).

Hepatic function and haematological parameters
The haematological parameters and the hepatic function must be monitored at regular intervals.

Carcinogenic potential
In humans, in the rare cases the appearance of acute leukaemia has coincided with use of cisplatin, which was in general associated with other leukaemogenic 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 teratogenetic 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. Special care is required for patients with acute bacterial or viral infections.

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.).

WARNING
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.

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, myelosuppression 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
This medicinal product contains less than 1 mmol sodium (9 mg) per ml, i.e. essentially 'sodium- free'.
This should be considered if a low sodium diet has to be kept.

4.5 Interaction with other medicinal products and other forms of interactions

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 renalfunction.

The renal toxicity of ifosphamide 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/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.

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 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.

Ifosphamide 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 regularly to check the INR.

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

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

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 anticonvulsive treatment with phenytoin is strictly contraindicated (see section 4.3.).

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 (in 70% of patients or more).

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 tumours, docetaxel in combination with cisplatin induced more severe neurotoxic effects (dose-related and predominantly sensory type neuropathy)) 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 carcinogenicity (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 when patients wish to have children after treatment with cisplatin. 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 (like nephrotoxicity) may influence the ability to drive and use machines. Patients who suffer from these effects (eg 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, 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).

Table of Adverse Drug Events Reported During Clinical or Post marketing Experience (MedDRA terms).

System Organ Class	Frequency	M ed DRA T erm
Infections and infestations	Common	Sepsis
	Not known	Infection[a]
Neoplasm benign, malignant, and unspecified (incl cysts and polyps)	Rare	Acute leukaemia
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia
Immune system disorders	Uncommon	Anaphylactoid[b] reaction
	Rare	Immunosuppression
Endocrine disorders	Not known	Blood amylase increased, inappropriate antidiurectic hormone secretion
Metabolism and nutrition disorders	Very common	Hyponatraemia
	Uncommon	Hypomagnesaemia
	Rare	hypercholestrerolemia
	Not known	Dehydration, hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalcaemia, tetany
Nervous system disorders	Common	Neurotoxicity
	Rare	Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
	Very rare	Seizures
	Not known	Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
Eye disorders	Rare	Optic retrobulbar neuritis, impaired eye movement

System Organ Class	Frequency	M ed DRA T erm
	Not known	Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilloedema, retinal pigmentation
Ear and labyrinth disorders	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
	Rare	Hypertension
	Not known	Thrombotic microangiopathy (haemolytic uraemic syndrome), Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, pneumonia and respiratory failure
	Not known	Pulmonary embolism
Gastrointestinal disorders	Rare	Stomatitis
	Not known	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 and pain
	Not known	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Not known	Muscle spasms
Renal and urinary disorders	Very common	Renal failure acute, renal failure[c], renal tubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis and ovulation, gyneacomastia
General disorders and administration site condition	Not known	Pyrexia (very common), asthenia, malaise, injection site extravasation[d]

System Organ Class	Frequency	M ed DRA T erm
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 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.

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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

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

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

There is no specific antidote in the event of an overdose 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 inhibits DNA-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
In chronic toxicity models indications for renal damage, bone marrow depression, gastro intestinal disorders and ototoxicity have been observed.

Genotoxicity and carcinogenicity
Cisplatin is genotoxic in numerous in vitro and in vivo tests (bacterial test systems, chromosomal disorders in animal cells and in tissue cultures). In long-term studies it has been shown that cisplatin is carcinogenic in mice and rats.

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 have shown that exposure during pregnancy can cause tumours in adult offspring. Cisplatin is embryotoxic in mice and rats, and in both species deformities have been reported. Cisplatin is excreted in the breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium chloride
Hydrochloric acid for pH adjustment
Sodium hydroxide for pH adjustment

6.2 Incompatibilities

Do not bring this medicinal product 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.

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Before opening: 2 years

After dilution

Chemical and physical in-use stability has been demonstrated for 8 hours at 15-25°C in ambient light and for 14 days at 15-25°C under protection from light.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in use storage and times conditions are the responsibility of user. The diluted solution should be protected from light. Do not store diluted solutions in the refrigerator or freezer.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Keep the vial in the outer carton in order to protect from light. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used.

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

6.5 Nature and contents of container

The vial contains either 10 ml, 20 ml, 50 ml or 100 ml concentrate for solution for infusion.

The vial containing 10 ml concentrate in a 20 ml moulded amber coloured type I glass vial with chlorobutyl rubber stopper and sealed with green flip-off aluminium seal.

The vial containing 20 ml concentrate in a 20 ml moulded amber coloured type I glass vial with chlorobutyl rubber stopper and sealed with red flip-off aluminium seal.

The vial containing 50 ml concentrate in a 50 ml moulded amber coloured type I glass vial with chlorobutyl rubber stopper and sealed with yellow flip-off aluminium seal.

The vial containing 100 ml concentrate in a 100 ml moulded amber coloured type I glass vial with chlorobutyl rubber stopper and sealed with purple flip-off aluminium seal.

Pack Sizes:
1 x 10 ml vial
1 x 20 ml vial
1 x 50 ml vial
1 x 100 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Preparation and handling of the product
Refer to local cytotoxic guidelines.

Like with all anti-neoplastic products caution is needed with the processing of cisplatin. Dilution should take place under aseptic conditions in a safety box, by trained personnel in an area specifically intended for this, and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses. 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.

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.

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 9 mg/ml (0.9%)
§ mixture of sodium chloride 9 mg/ml (0.9%)/ glucose 50 mg/ml (5%) (1:1), (resulting final concentrations: sodium chloride 4.5 mg/ml (0.45%), glucose 25 mg/ml (2.5%))

Always look at the injection before use. 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 chemical and physical stability with use of the undiluted solutions, see section 6.3.

For single use only. Discard any unused contents in accordance with local cytotoxic guidelines

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.

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. Remnants of the medicinal products as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents and in accordance with local requirements related to the disposal of hazardous waste.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/033/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 2nd May 2014

10 DATE OF REVISION OF THE TEXT

April 2019
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