

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 50 ml concentrate for solution for infusion contains 50 mg of cisplatin.

Excipient with known effect:

Each ml of solution contains 3.5 mg (< 1mmol) of sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, slightly yellow solution free from visible particles.

The pH is between 3.5 and 6.5.

The osmolarity is 287 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

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.).

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 a 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/m² body surface every 3 to 4 weeks;
- 15 to 20 mg/m²/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/m² 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/m² 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%.

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 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 administered 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.

4.3 Contraindications

Cisplatin is contraindicated in patients:

- with hypersensitivity to cisplatin or other platinum compounds or to any of the excipients listed in section 6.1;
- with renal dysfunction (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 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)

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/µl or > 4.0 x 10⁹/l
- Blood platelets > 100.000/µl or > 100 x 10⁹/l
- Audiogram: results within the normal range.

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 (e.g., 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 50mg/m², and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000Hz). 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).

Audiograms must be made before starting treatment with cisplatin and always before starting another treatment cycle (see section 4.8).

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 sections 4.3 and 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 teratogenic and embryotoxic 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.

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 contains 3.5 mg sodium per ml. This should be considered if a low sodium diet has to be kept.

4.5 Interaction with other medicinal products and other forms of interactionNephrotoxic 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 ifosfamide 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/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 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 anticonvulsant 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:

Evidence has been established that the treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 70-75% 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 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

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.

Breastfeeding

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

Fertility

Cisplatin can cause temporary or permanent infertility. Genetic consultation is recommended when patients wish to have children after treatment with cisplatin. Sperm cryopreservation can be considered (see also section 4.4).

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.

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 (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, 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$), 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 |
|------------------------------------|-----------|------------------------|
| <i>Infections and infestations</i> | Common | Sepsis |
| | Not known | Infection ^a |
| | | |

| | | |
|--|-------------|---|
| <i>Neoplasm benign, malignant, and unspecified</i> | Rare | Acute leukaemia |
| <i>Blood and lymphatic system disorders</i> | Very common | Bone marrow failure, thrombocytopenia, leukopenia, anaemia |
| | Very rare | Thrombotic microangiopathy combined with haemolytic uraemic syndrome |
| | Not known | Coombs positive haemolytic anaemia |
| <i>Immune system disorders</i> | Uncommon | Anaphylactoid ^b reaction |
| | Rare | Immunosuppression |
| <i>Endocrine disorders</i> | Not known | Blood amylase increased, inappropriate antidiuretic hormone secretion |
| <i>Metabolism and nutrition disorders</i> | Very common | Hyponatraemia |
| | Uncommon | Hypomagnesaemia |
| | Rare | Hypercholesterolemia |
| | Very rare | Increased blood iron |
| | Not known | Dehydration, , hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalcaemia, tetany |
| <i>Nervous system disorders</i> | 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 |
| <i>Eye disorders</i> | Rare | Optic retrobulbar neuritis, impaired eye movement |
| | Not known | Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilloedema, retinal pigmentation |
| <i>Ear and labyrinth disorders</i> | Uncommon | Ototoxicity |
| | Not known | Tinnitus, deafness |
| <i>Cardiac disorders</i> | Common | Arrhythmia, bradycardia, tachycardia |
| | Rare | Myocardial infarction, severe coronary artery disease |
| | Very rare | Cardiac arrest |
| | Not known | Cardiac disorder |
| <i>Vascular disorders</i> | Common | Phlebitis |
| | Rare | Hypertension |
| | Not known | Thrombotic microangiopathy (haemolytic uraemic syndrome), Raynaud's phenomenon |
| <i>Respiratory, thoracic and mediastinal disorders</i> | Common | Dyspnoea, pneumonia and respiratory failure |
| | Not known | Pulmonary embolism |
| | | |

| | | |
|--|-------------|--|
| <i>Gastrointestinal disorders</i> | Rare | Stomatitis |
| | Not known | Vomiting, nausea, anorexia, hiccups, diarrhoea |
| <i>Hepatobiliary disorders</i> | Not known | Hepatic enzymes increased, blood bilirubin increased |
| <i>Skin and subcutaneous tissue disorders</i> | Common | Erythema, skin ulcer, localised oedema and pain |
| | Not known | Rash, alopecia |
| <i>Musculoskeletal, connective tissue and bone disorders</i> | Not known | Muscle spasms |
| <i>Renal and urinary disorders</i> | Very common | Renal failure acute, renal failure ^c , renal tubular disorder |
| <i>Reproductive system and breast disorders</i> | Uncommon | Abnormal spermatogenesis and ovulation, gynecomastia |
| <i>General disorders and administration site condition</i> | Not known | Pyrexia (very common) , asthenia, malaise, injection site extravasation ^d |
| <i>Investigations</i> | 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 preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost'. Alternatively, the traditional post-paid 'yellow card' option may also continue to be used.

FREEPOST

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

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.

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, gastrointestinal 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium chloride
Hydrochloric acid for pH adjustment

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.

Antioxidants (such as sodium metabisulphite), bicarbonates (sodium bicarbonate), sulphates, 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: 18 months, at maximum 25°C, in the original package.

After dilution in infusion fluids described in section 6.6:

Chemical and physical in-use stability has been demonstrated for 24 hours at 15°C-25°C. From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination the product should always be used immediately.

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 storage conditions after dilution of the medicinal product: see section 6.3. Do not store diluted solutions in the refrigerator or freezer.

6.5 Nature and contents of container

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

The vial containing 10 ml concentrate is an 11 ml brown coloured type I glass vial with bromobutyl rubber stop and sealed with aluminium metallic cap with flip off.

Vial will be packed with or without a protective plastic overwrap.

The vial containing 50 ml concentrate is a 50 ml brown coloured type I glass vial with bromobutyl rubber stop and sealed with aluminium metallic cap with flip off.

Vial will be packed with or without a protective plastic overwrap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

The required volume of the drug product solution will be introduced into the PE bottle containing the following solutions:

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

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.

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.

With respect to microbiological, 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

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

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8 MARKETING AUTHORISATION NUMBER

PA1399/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th October 2013

10 DATE OF REVISION OF THE TEXT

March 2017