Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cisplatin Teva 1 mg/ml, concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cisplatin Teva 1 mg/ml concentrate for solution for infusion contains 1 mg/ml of cisplatin.

Each ml of solution contains 3.5 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, light yellow solution free from visible particles

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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/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/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.

Special patient population
In patients with renal dysfunction or bone marrow depression, the dose should be reduced adequately.

Hydration
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 200 ml/hour for a period of 6 to 12 hours, with a total amount of at least 1 L.

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 37.5 g 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
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.

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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or other platinum-containing compounds.

Cisplatin is contraindicated in patients with myelosuppression, with neuropathy caused by cisplatin, in patients who are dehydrated (pre- and post-hydration is required to prevent serious renal dysfunction), and those with pre-existing renal impairment (creatinine clearance < 60 ml/min) or hearing impairment due to the fact that cisplatin is nephrotoxic and neurotoxic (in particular ototoxic). These toxicities may be cumulative if disorders of this type pre-exist.

Patients receiving cisplatin should not breastfeed.

Concurrent administration of yellow fever vaccine is contraindicated (see section 4.5).

Concurrent prophylactic use of phenytoin is contraindicated (see section 4.5).

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 specialised 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.

Before, during and after administration of cisplatin, the following parameters resp. organ functions 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).

These examinations must be repeated every week over the entire duration of the treatment with cisplatin.

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.

Nephrotoxicity
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).
Forced diuresis by hydration or by hydration and suitable diuretics before and after the cisplatin administration decreases the risk of nephrotoxicity. Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin-induced nephrotoxicity.

Neuropathies
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/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). Audiograms must be made before starting treatment with cisplatin and always before starting another treatment cycle.

Allergic phenomena
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).
Anaphylactic-like reactions to cisplatin have been observed. These reactions can be controlled by administration of antihistamines, adrenaline and/or glucocorticoids.

Hepatic function and haematological formula
The haematological formula 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 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.

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

Cisplatin is proven to be cumulative ototoxic, nephrotoxic, and neurotoxic. 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.

Renal toxicity, which is above-all cumulative, is severe and requires particular precautions during administration (see sections 4.2 and 4.8).

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.
Nausea and vomiting may be intense and require adequate anti-emetic 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.

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.

This medicinal product contains 3.5 mg (0.154 mmol) sodium per ml solution. To be taken into consideration by patients on a controlled sodium diet.

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. 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).

Pyridoxine + 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.

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

Fertility
Since a treatment with cisplatin may cause irreversible infertility, it is recommended that men, who wish to become fathers in the future, ask for advice regarding cryoconservation of their sperm prior to treatment.

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

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

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

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

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

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Nevertheless, the profile of undesirable effects (like nephrotoxicity, central nervous system and special senses) may influence the ability to drive vehicles and use machinery.
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 used dose and may have cumulative effects.

The most frequently reported adverse events (>10%) of cisplatin were haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricaemia) and fever.

Serious toxic effects on the kidneys, bone marrow and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative. Ototoxicity may be more severe in children.

Frequencies are defined using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Infections and infestations
Common: Infections[a], sepsis.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Rare: Acute leukaemia. Cisplatin increases the risk of secondary leukaemia. The risk of secondary leukaemia is dose-dependent and not age- and sex-related. Carcinogenicity is theoretically possible (based on cisplatin's mechanism of action).

Blood and lymphatic system disorders
Very common: Dose dependent, cumulative and mostly reversible leukopenia, thrombocytopenia and anaemia are observed in 25-30% of patients treated with cisplatin. Bone marrow failure.
Common: A considerable decrease in the number of white blood cells often occurs approximately 14 days after the use (less than 1.5×10^9/l in 5% of the patients). A decrease of the number of platelets is observed after approximately 21 days (less than 10% of the patients showed a total less than 50×10^9/l) (the recovery period is approximately 39 days). Anaemia (decreases of greater than 2g haemoglobin) occurs at approximately the same frequency, but generally with a later onset than leukopenia and thrombocytopenia.
Rare: Coombs positive haemolytic anaemia was reported and was reversible if the use of cisplatin was terminated. Literature has been published regarding hemolysis possibly caused by cisplatin. Serious bone marrow failure (including agranulocytosis and/or aplastic anaemia) may occur after high doses of cisplatin.

Immune system disorders
Uncommon: Hypersensitivity may present as rash, urticaria, erythema, or pruritus allergic.
Rare: Anaphylactic reactions have been reported; hypotension, tachycardia, dyspnoea, bronchospasm, facial oedema (PT-face oedema), and fever have been reported.
Treatment with antihistamines, epinephrine (adrenaline) and steroids may be required.
Immunosuppression has been documented.

Endocrine disorders
Rare: Blood amylase increased.
Very rare: Syndrome of inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders
Very common: Hyponatraemia
Uncommon: Hypomagnesaemia
Rare: Hypocalcaemia, hypophosphataemia and hypokalaemia with muscle spasms and/or electrocardiogram changes occur as a result of damage to the kidney caused by cisplatin, thus reducing the tubular resorption of cations. Hypercholesterolemia.
Very rare: Increased blood iron.
Not known: Dehydration, hyperuricaemia, tetany

Nervous system disorders
Common: Neurotoxicity caused by cisplatin is characterised by peripheral neuropathy (typically bilateral and sensory), and rarely by the loss of taste or tactile function, or by optic retrobulbar neuritis with reduced visual acuity and cerebral dysfunction (confusion, dysarthria, individual cases of cortical blindness, loss of memory, paralysis). Lhermitte's sign, autonomous neuropathy and myelopathy of the spinal cord have been reported.
Rare: Cerebral disorders (including acute cerebrovascular complications, cerebral arteritis, occlusion of the carotic artery, and encephalopathy), convulsion, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome.
Very rare: Seizures.

Not known: Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke, ageusia.

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

Eye disorders
Rare: Blindness during a combination treatment with cisplatin. Following high-dose cisplatin application impairment of colour vision and eye movement has been reported.
Very rare: Papilloedema, optic neuritis and cortical blindness have been reported following treatment with cisplatin. One case of unilateral optic neuritis retrobulbar with reduced visual acuity has been reported after combination chemotherapy followed by cisplatin treatment.
Not known: Vision blurred, colour blindness acquired, retinal pigmentation.

Ear and labyrinth disorders
Very common: Hearing impairment has been documented in approximately 31% of patients treated with 50 mg/m^2 cisplatin. The defect is cumulative, may be irreversible, and is sometimes limited to one ear. Ototoxicity manifests itself as tinnitus and/or hearing impairment at higher frequencies (4,000-8,000 Hz). Hearing impairment at frequencies of 250-2,000 Hz (normal hearing range) was noticed for 10 to 15% of the patients.
Common: Deafness and vestibular toxicity combined with vertigo may occur. Prior or simultaneous cranial radiation increases the risk of hearing loss.
Rare: Patients may lose the ability to conduct a normal conversation. Cisplatin-induced hearing impairment may be serious for children and elderly patients. (See section 4.4).

Cardiac disorders
Common: Arrythmia including bradycardia, tachycardia and other electrocardiogram changes e.g. ST-segment changes, signs of myocardial ischemia have been observed particularly in combination with other cytotoxics.
Rare: Hypertension and myocardial infarction may occur, even some years after chemotherapy. Severe coronary artery disease.
Very rare: Cardiac arrest has been reported after treatment with cisplatin combined with other cytotoxics.
Not known: Cardiac disorder.

Vascular disorders
Common: Phlebitis may occur in the area of the injection after intravenous administration.
Very rare: Vascular disorders (cerebral or myocardial ischaemia, impairment of the peripheral circulation related to the Raynaud's syndrome) were linked to cisplatin chemotherapy.
Not known: Thrombotic microangiopathy (haemolytic uraemic syndrome).

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, pneumonia and respiratory failure.
Not known: Pulmonary embolism.

Gastrointestinal disorders
Very common: Anorexia, nausea, vomiting and diarrhoea occur between 1 and 4 hours after the use of cisplatin. (See section 4.4)
Uncommon: Metallic setting on the gums.
Rare: Stomatitis.

Hepatobiliary disorders
Common: Abnormal hepatic function with increased transaminases and blood bilirubin are reversible.
Rare: Reduced blood albumin levels were noticed and may be linked to the treatment with cisplatin.

Skin and subcutaneous tissue disorders
Common: Erythema and skin ulcer may occur in the area of the injection after intravenous administration.
Uncommon: Alopecia.
Not known: Rash.

Musculoskeletal and connective tissue disorders
Not known: Muscle spasms.

Renal and urinary disorders
Very common: Renal failure[b] after single or multiple doses of cisplatin. A mild, reversible renal dysfunction may be observed after a single intermediary dose of cisplatin (20 mg/m^2 to < 50 mg/m^2). The use of a single high dose (50-120 mg/m^2), or repeated daily use of cisplatin, may cause renal failure with tubular renal necrosis presenting as uraemia or anuria. Renal failure may be irreversible.
The nephrotoxicity is cumulative and may occur 2-3 days, or two weeks after the first dose of cisplatin. Serum creatinine and urea concentrations may increase. Nephrotoxicity was observed in 28-36% of patients without sufficient hydration after a single dose of 50 mg/m^2 of cisplatin (See section 4.4). Hyperuricaemia occurs asymptomatically or as gout. Hyperuricaemia has been reported in 25-30% of patients in conjunction with nephrotoxicity. Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin-induced nephrotoxicity.
Not known: Renal failure acute.

Reproductive system and breast disorders
Uncommon: Abnormal spermatogenesis and ovulation, and painful gynaecomastia.

General disorders and administration site conditions
Very common: Fever.
Common: Injection site extravasation[c].
Uncommon: Hiccups, asthenia, malaise.

[a] Infectious complications have led to death in some patients.
[b] Elevations in BUN and creatinine, serum uric acid, and/or a decrease in creatinine clearance are subsumed under renal insufficiency/failure.
[c] 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

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

Treatment in the event of an overdose consists of general support measures.

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

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.
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 5.3 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.

Mutagenicity and carcinogenicity
Cisplatin is mutagenic 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 1N for pH adjustment
Sodium hydroxide 1N 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.
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.

6.3 Shelf life

Before opening
- 10 ml: 18 months
- 50 ml: 3 years
- 100 ml: 3 years

After dilution
After dilution in infusion fluids described in section 6.6, the product can be stored for at most 14 days at room temperature (15°C–25°C) under protection from light. Do not store diluted solutions in the refrigerator or freezer.

Exposure to ambient light must be limited to at most 6 hours. If exceeding 6 hours, the bags must be thoroughly wrapped in aluminium foil in order to protect the contents from ambient light.

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.

6.4 Special precautions for storage

Undiluted solution: Store at 15°C-25°C. Keep container in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Brown, type I glass vials of 10, 50 and 100 ml with butyl rubber stop, with aluminium closing and plastic snap-cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation and handling of the product
Like with all anti-neoplastic products caution is needed with the processing of cisplatin. Dilution should take place under aseptic conditions by trained personnel in an area specifically intended for this. Protective gloves should be worn for this. Precautions should be taken to avoid contact with the skin and mucous membranes. If skin contact did occur anyway, the skin should be washed with soap and water immediately.

With skin contact tingling, burns and redness have been observed. In case of contact with the mucous membranes they should be copiously rinsed with water. After inhalation dyspnoea, pain in the chest, throat irritation and nausea have been reported.

Pregnant women must avoid contact with cytostatic drugs.

Bodily waste matter and vomit should be disposed with care.

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

A damaged bottle must be regarded and treated with the same precautions as contaminated waste. Contaminated waste must be stored in waste containers specifically marked for this.

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

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

Always look at the injection before use. 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.

For microbiological, chemical and physical stability of the undiluted and diluted solutions, see sections 6.3 and 6.4.

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

Teva Pharma B.V.
Swensweg 5
2031GA Haarlem
The Netherlands

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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