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.

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

Excipients with known effect:
Cisplatin 10 mg/10 ml (1 mg/ ml) concentrate forsolution for infusion contains 35.4 mg of sodium in each 10 ml vial.
Cisplatin 50 mg/50 ml (1 mg/ ml) concentrate for solution for infusion contains 177 mg of sodium in each 50 ml vial.
Cisplatin 100 mg/100 ml (1 mg/ ml) concentrate for solution for infusion contains 354 mg of sodium in each 100 ml vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for Infusion.

Clear, colourless to pale yellow solution free fromvisible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cisplatin is intended for the treatment of:

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

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

Cisplatin can be used as monotherapy and in combination therapy

4.2 Posology and method of administration

Posology

ADULTS AND 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.

Method of administration

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 therapy, the dose of cisplatin must be reduced. A typical dose is 20mg/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 warning and precautions to be considered prior to the start of the next treatment cycle
(see section 4.4).

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

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).

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 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.

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

The dilution 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.

4.3 Contraindications

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

- Cisplatin induces nephrotoxicity which is cumulative. It is therefore contraindicated in patients with pre-existing renal impairment.

- Cisplatin has also been shown to be cumulatively neurotoxic (in particular ototoxic) and should not be given to patients with pre-existing hearing impairment.

- Cisplatin is also contraindicated in myelosuppressed patients and those who are dehydrated.

- Patients receiving cisplatin must not breast-feed.

- Concurrent administration of yellow fever vaccine is contraindicated.

4.4 Special warnings and precautions for use

Cisplatin is a highly toxic drug with a relatively narrow therapeutic index, and a therapeutic effect is unlikely to occur without some evidence of toxicity. This cytostatic agent has a more marked toxicity than is usually found in antineoplastic chemotherapy.

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing I.V. sets, needles, catheters and syringes must be avoided. Before administering the solution to the patient, verify the clarity of the solution and the absence of particles.

Cisplatin solution for infusion should not be mixed with other drugs or additives.

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

Nephrotoxicity
Cisplatin produces severe cumulative nephrotoxicity which may be potentiated by aminoglycoside antibiotics. Cisplatin should not be given more frequently than once every 3-4 weeks.

To maintain urine output and reduce renal toxicity it is recommended that cisplatin be administered as an intravenous infusion over 6 to 8 hours (see section 4.2).

Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100 ml (130 µmol/l) or blood urea nitrogen (BUN) below 25 mg/100 ml (9 mmol/l), and circulating blood levels are at an acceptable level. Since the renal toxicity of cisplatin is cumulative, measurement of BUN, serum creatinine or Glomerular Filtration Rate (GFR)/Creatinine Clearance Rate (CCr) should be performed prior to initiating therapy and prior to each subsequent course.

Adequate pre-treatment and 'during treatment' hydration should be ensured to minimise hazards of renal toxicity. A urine output of 100 ml/hour or greater will tend to minimise cisplatin nephrotoxicity. This can be accomplished by pre-hydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration treatment (recommended 2,500 ml/m^2 BSA/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g. 10% mannitol solution).

Special care has to be taken when cisplatin-treated patients are given concomitant therapies with other potentially nephrotoxic drugs (see section 4.5).

Bone marrow function
Peripheral blood counts should be monitored frequently in patients receiving cisplatin. Although the hematologic toxicity is usually moderate and reversible, severe thrombocytopenia and leukopenia may occur. In patients who develop thrombocytopenia special precautions are recommended: care in performing invasive procedures; search for signs of bleeding or bruising; test of urine, stools and emesis for occult blood; avoiding aspirin and other NSAIDs. Patients who develop leukopenia should be observed carefully for signs of infection and might require antibiotic support and blood product transfusions. See section 4.8.

Central Nervous System function

Cisplatin is known to induce neurotoxicity. Therefore, neurologic examination at regular intervals is warranted in patients receiving a cisplatin-containing treatment.

Severe cases of neuropathies have been reported.

These neuropathies may be irreversible and may manifest by paraesthesia, areflexia, proprioceptive loss and a loss of vibration perception. A loss of motor function has also been reported. Since neurotoxicity may result in irreversible damage, it is recommended to discontinue therapy with cisplatin when neurologic toxic signs or symptoms become apparent. See section 4.8.

Ototoxicity
Cisplatin may produce cumulative ototoxicity, which is more likely to occur with high-dose regimens. Audiometry should be performed prior to initiating therapy, and repeated audiograms should be performed when auditory symptoms occur or clinical hearing changes become apparent. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. Vestibular toxicity has also been reported. (see section 4.8).

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.

Cases of delayed-onset hearing loss have been reported in the paediatric population. Long term follow-up in this population is recommended. 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.

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

Allergic phenomena
As with other platinum-based products, hypersensitivity reactions may occur, appearing in most cases during perfusion necessitating discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

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

Carcinogenic potential
In humans, in rare cases the appearance of acute leukaemia has coincided with the use of cisplatin, which was in general associated with other leukaemogenic agents.

Cisplatin is carcinogenic in mice and rats (see section 5.3).

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.

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

Immunosuppressant effects/ Increased susceptibility to infections.
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cisplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cisplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished

Excipient information
Cisplatin 10 mg/10 ml (1 mg/ ml) concentrate for solution for infusion contains 35.4 mg of sodium in each 10 ml vial, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cisplatin 50 mg/50 ml (1 mg/ ml) concentrate for solution for infusion contains 177 mg of sodium in each 50 ml vial, equivalent to 8.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cisplatin 100 mg/100 ml (1 mg/ ml) concentrate for solution for infusion contains 354 mg of sodium in each 100 ml vial, equivalent to 17.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cisplatin may be further prepared for administration with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

Cisplatin can be used in combination with other cytostatics with corresponding mechanisms of action. Additive toxicity might occur in such cases.

Myelosuppression induced by cisplatin will be additive to existent impairment or to the similar toxicity of other agents such as cephaloridine, frusemide, aminoglycosides, etc., administered concurrently.

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. *Nephrotoxicity* might be exacerbated by aminoglycoside antibiotics, administered simultaneously or 1-2 weeks after treatment with cisplatin. The use of other potentially nephrotoxic drugs (e.g. amphotericin) is not recommended during treatment with cisplatin. 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.

Renally excrete ddrugs
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.

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.

Ifosfamide may increase hearing loss due to cisplatin.

Weakened livev accines
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.

Oral anticoagulants
In the event of simultaneous use of oral anticoagulants such as coumarins/warfarin, it is advisable to regularly check the INR.

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

Pyroxidine + altretamine combination
During a randomised study of the treatment of advanced ovarian cancer, the response time was unfavourably affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

Paclitaxel

Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity.

Anticonvulsant agents
In patients receiving cisplatin and anticonvulsants, plasma levels of anticonvulsant agents (e.g. phenytoin) may be decreased and potentially become subtherapeutic. This is probably as a result of decreased absorption and/or increased metabolism. In these patients, serum levels of anticonvulsants should be monitored and dosage adjustments made as necessary.

Cisplatin may interact with aluminium (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during treatment with cisplatin and for at least 29 weeks (at least 7 months) following the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with cisplatin and for at least 17 weeks (at least 4 months) after the last dose.

Pregnancy

Cisplatin should not be used unless there are no alternative safer treatment and treatment cannot be delayed until pregnancy has ended and the risk/benefit consideration for the individual patient support its use. Cisplatin may be toxic to the foetus when administered to a pregnant woman. The safe use of cisplatin in human pregnancy has not been established. The single role of cisplatin is not clear; thus, a causal association cannot be established based on the few case reports. However, considering the potential harm to the fetus when administered to a pregnant woman, cisplatin use in pregnant women is not recommended. Patients should be advised to avoid becoming pregnant. Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

Cisplatin and its active metabolites have been identified in human milk of treated mothers. Women should not breast-feed while undergoing treatment with cisplatin and for 4 weeks after the last dose of cisplatin.

Fertility

Female
Based on non-clinical (section 5.3) and clinical findings, female fertility may be compromised by treatment with cisplatin. Use of cisplatin has been associated with cumulative dose-
dependent ovarian failure, premature menopause and reduced fertility.

Male
Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported (section 4.8). Although the impairment of spermatogenesis can be reversible, males
undergoing cisplatin treatment should be warned about the possible adverse effects on male
fertility.

Both men and women should seek advice on fertility preservation before treatment.

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) may influence the ability to drive vehicles and use machinery.

4.8 Undesirable effects

The most frequently reported adverse events 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

System Organ Class	Frequency	Adverse Event
Infections and infestations	Common	Sepsis
	Not known	Infection[a]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Rare	Acute leukaemia
	Not known	Myelodysplastic syndromes[e]
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia, thrombotic microangiopathy (haemolytic uremic syndrome), neutropenia
Immune system disorders	Uncommon	Anaphylactoid[b] reaction
	Not known	Anaphylactic reaction
Endocrine disorders	Not known	Blood amylase increased, inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Very common	Hyponatraemia
	Uncommon	Hypomagnesaemia
	Not known	Dehydration, hypokalaemia, hypophosphataemia, hyperuricaemia, hypocalcaemia, tetany
Nervous system disorders	Rare	Convulsion, peripheral neuropathies, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
	Not known	Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke, ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
Eye disorders	Not known	Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilledema, retinal pigmentation
Ear and labyrinth disorders	Uncommon	Ototoxicity
	Not known	Tinnitus, deafness
Cardiac disorders	Common	Arrhythmia, bradycardia, tachycardia
	Rare	Myocardial infarction
	Very rare	Cardiac arrest
	Not known	Cardiac disorder, coronary artery disease, congestive heart failure
Vascular disorders	Common	Venous thromboembolism
	Not known	Raynaud's phenomenon, postural hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism, pulmonary toxicity[f]

Gastrointestinal disorders	Rare	Stomatitis
	Not known	Vomiting, nausea, anorexia, hiccups, diarrhoea
Hepatobiliary disorders	Not known	Hepatic enzymes increased[g], blood bilirubin increased
Skin and subcutaneous tissue disorders	Not known	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Not known	Muscle spasms, myalgia
Renal and urinary disorders	Not known	Renal failure acute, renal failure[c], renal tubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis
	Not known	Azoospermia
General disorders and administration site condition	Not known	Pyrexia (very common), asthenia, malaise, injection site extravasation[d]

a: Infectious complications have led to death in some patients.
b: Symptoms include facial oedema, flushing, wheezing, bronchospasm, tachycardia, and hypotension.
c: Elevations in BUN and creatinine, serum uric acid, and/or decrease in creatinine clearance are subsumed under renal insufficiency/failure.
d: Local soft tissue toxicity including cellulitis, fibrosis, and necrosis (common) pain (common), oedema (common), phlebitis and erythema (common) as the result of extravasation.
e: Mostly when given in combination with potentially leukemogenic agents.
f: Pulmonary toxicity has been reported in patients treated with cisplatin in combination with bleomycin or 5-fluorouracil.
g: Mild and transient elevations of serum AST and ALT levels may occur infrequently.

Renal and urinary disorders
Renal toxicity has been shown in 28-38% of patients treated with a single dose of cisplatin 50 mg/m^2. Renal toxicity becomes more prolonged and severe with repeated courses of the drug.

Acute renal toxicity, which was highly frequent in the past and represented the major dose-limiting toxicity of cisplatin, has been greatly reduced by the use of 6 to 8-hour infusions as well as by concomitant intravenous hydration and forced diuresis. Cumulative toxicity, however, remains a problem and may be severe. Renal impairment, which is associated with tubular damage, may be first noted during the second week after a dose and is manifested by an increase in serum creatinine, BUN, serum uric acid and/or a decrease in creatinine clearance. Renal insufficiency is generally mild to moderate and reversible at the usual doses of the drug (recovery occurring as a rule within 2-4 weeks); however, high or repeated cisplatin doses can increase the severity and duration of renal impairment and may produce irreversible renal insufficiency (sometimes fatal). Renal failure has been reported also following intraperitoneal instillation of the drug.

Gastrointestinal disorders
Nausea and vomiting occur in the majority of patients, usually starting within 1 hour of treatment and lasting up to 24 hours or longer. These side effects are only partially relieved by standard antiemetics. The severity of these symptoms may be reduced by dividing the total dose per cycle into smaller doses given once daily for five days. Reported toxicity includes gingival platinum line.

Anorexia, nausea and occasional vomiting may persist for up to a week.

Eye disorders
There have been reports of optic neuritis, papilledema and cortical blindness following treatment with cisplatin. Improvement and/or total recovery usually occurs following immediate discontinuation. Blurred vision and altered colour perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended.

Ear and labyrinth disorders
Ototoxicity has occurred in up to 31% of patients treated with a single dose of cisplatin at 50 mg/m^2 BSA. The damage to the hearing system appears to be dose-related and cumulative, and it is reported more frequently in very young and very old patients. Careful monitoring should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Unilateral or bilateral tinnitus, which is usually reversible, and/or hearing loss in the high frequency range may occur.

The overall incidence of audiogram abnormalities is 24%, but large variations exist. These abnormalities usually appear within 4 days after drug administration and consist of at least a 15 decibel loss in pure tone threshold. The damage seems to be cumulative and is not reversible. The audiogram abnormalities are most common in the 4000-8000 Hz frequencies.

Cases of delayed-onset hearing loss have been reported in the paediatric population (see section 4.4). Delayed onset occurring months/ years after administration has also been reported.

Blood and lymphatic system disorders
Myelosuppression is observed in about 30% of patients treated with cisplatin but is mostly mild to moderate and reversible at the usual doses. Leukopenia and thrombocytopenia are dose-related and are more pronounced at higher doses or in patients who have received prior myelosuppressive treatments. The nadirs in circulating platelets and leucocytes generally occur between days 18-23 (range 7.3 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at doses greater than 50 mg/m^2 BSA. Anaemia (decreases of greater than 2 g% haemoglobin) occurs at approximately the same frequency, but generally with a later onset than leukopenia and thrombocytopenia. Subsequent courses of cisplatin should not be instituted until platelets are present at levels greater than 100,000/mm^3 and white cells greater than 4,000/mm^3. A high incidence of severe anaemia requiring transfusion of packed red cells has been observed in patients receiving combination chemotherapy including cisplatin.

Immune system disorders
Reactions possibly secondary to cisplatin therapy have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are particularly at risk are those with a prior history or family history of atopy. Facial oedema, wheezing, tachycardia, hypotension and skin rashes of urticarial non-specific maculopapular type can occur within a few minutes of administration. Serious reactions seem to be controlled by I.V. adrenaline, corticosteroids or antihistamines.

Nervous system disorders
Neurotoxicity may occur. It is cumulative and may be irreversible, however it has also been partially or completely reversible following discontinuance of cisplatin therapy. It is generally characterised by neuropathies. Peripheral neuropathies occur infrequently with usual doses of the drug.

Peripheral neuropathies are generally sensory in nature, including paraesthesia in both upper and lower extremities, motor difficulties, reduced reflexes and leg weakness and tremor. Autonomic neuropathy, seizures, slurred speech, loss of taste and memory loss have also been reported. These neuropathies usually appear after prolonged therapy, but have also developed after a single drug dose.

Metabolism and nutrition disorders Hypomagnesaemia occurs quite frequently with cisplatin administration, while hypocalcaemia occurs less frequently. The loss of magnesium seems to be associated with renal tubular damage which prevents resorption of this cation. Hypomagnesemia and/or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm, and/or tetany. It does not appear to be dose related. Monitoring of electrolytes is necessary.

Hyponatraemia, hypokalaemia and hypophosphatemia can occur.

Hyperuricaemia occurring with cisplatin is more pronounced with doses greater than 50 mg/m^2 BSA. Allopurinol effectively reduces uric acid levels.

Cardiac and vascular disorders
Cardiac reactions including tachycardia and arrhythmia have been reported. Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. These events may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (Haemolytic uremic syndrome) or cerebral arteritis.

Other toxicities

There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine and with or without cisplatin. It has been suggested that hypomagnesaemia developing with the use of cisplatin may be an added, although not essential factor, associated with this event. The cause of this Raynaud's phenomenon is however currently unknown.

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. Website: www.hpra.ie.

4.9 Overdose

CAUTION IS ESSENTIAL IN ORDER TO PREVENT AN INADVERTENT OVERDOSE.

Acute overdosage with cisplatin may result in an enhancement of its expected toxic effects such as renal failure, liver failure, severe neurosensorial toxicities (deafness), ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. Death may also occur. 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.

There is no specific antidote in the event of an overdosage of cisplatin. Haemodialysis is only effective, even then partially, up to 3 hours after administration. If haemodialysis is initiated 4 hours after the overdose, it has little effect on the elimination of cisplatin from the body due to rapid and extensive binding of platinum to plasma proteins.

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

If fever develops during prolonged myelosuppression, appropriate presumptive antibiotic coverage should be instilled after cultures have been obtained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Antineoplastic Agents
ATC code: L01XA01

Cisplatin is a platinum-containing antineoplastic agent. Cisplatin has biochemical properties similar to those of bifunctional alkylating agents. The drug inhibits DNA synthesis by producing intrastrand and interstrand cross links in DNA. Protein and RNA synthesis are also inhibited to a lesser extent.

Although the principal mechanism of action of cisplatin appears to be inhibition of DNA synthesis, other mechanisms, including enhancement of tumour immunogenicity, may be involved in its antineoplastic activity. Cisplatin also has immunosuppressive, radio sensitising, and antimicrobial properties.

Cisplatin does not appear to be cell cycle or phase specific. Besides tumour cells, the target tissues are mainly those characterised by rapid cell proliferation such as bone marrow, gastrointestinal mucosa and gonads.

5.2 Pharmacokinetic properties

Absorption
There is good uptake of cisplatin by the kidneys, liver and intestine. More than 90% of platinum containing species remaining in the blood are bound (possibly irreversibly) to
plasma proteins. Penetration into the CSF is poor although significant amounts of cisplatin
can be detected in intracerebral tumours.

The clearance of total platinum from plasma is rapid during the first four hours after intravenous administration, but then proceeds more slowly because of covalent binding to serum proteins. Levels of unbound platinum fall with a half-life of 20 minutes to 1 hour depending on the rate of drug infusion.

Elimination
The elimination of intact drug and various platinum-containing biotransformation products is via the urine. About 15-25% of administered platinum is rapidly excreted in the first 2-4 hours after administration of cisplatin. This early excretion is mostly of intact cisplatin. In the first 24 hours after administration, 20-80% is excreted; the remainder representing drug bound to tissues or plasma protein. Studies aiming at determining plasma elimination half- life of total platinum have shown a very large interindividual and interstudy variation. Most studies reported a half-life of total plasma platinum post cisplatin treatment of approximately
5 days or longer.

5.3 Preclinical safety data

In non-clinical repeat dose toxicity studies, renal damage, bone marrow depression, gastrointestinal disorders, ototoxicity, neurotoxicity, and immunosuppression have been observed at exposure levels similar to clinical exposure levels.

Non-clinical data indicate cisplatin is mutagenic, genotoxic and carcinogenic. Thymic lymphomas, mammary adenocarcinomas, fibro-liposarcoma, and lung adenomas were reported from repeat-dose studies of up to 19 weeks duration in mice. Leukemia and renal fibrosarcoma were reported from repeat-dose studies of up to 3 weeks in rats.

Non-clinical studies in mice showed that cisplatin caused direct damage to primordial follicle oocytes, leading to apoptosis, and ovarian depletion. Cisplatin causes testis damage and decreased sperm counts in mice, primarily through effects on differentiated spermatogonia. These findings suggest potential clinically relevant effects on male and female fertility.

Developmental toxicity studies indicate cisplatin is embryotoxic in mice and rats, and teratogenic in both species at exposure levels similar to clinical exposure levels.

Studies in rodents have shown that exposure during pregnancy can cause tumours in adult offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium chloride
Dilute hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

There is a total loss of cisplatin in 30 minutes at room temperature when mixed with metoclopramide and sodium metabisulphite in concentrations equivalent to those that would be found on mixing with a commercial formulation of metoclopramide.

Cisplatin and sodium metabisulphite have been known to react chemically. Such antioxidants might inactivate cisplatin before administration if they are present in intravenous fluids.

Interaction with aluminium:

Cisplatin may interact with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes must be avoided.

6.3 Shelf life

Prior to first use: 24 months
In use: see section 6.4

6.4 Special precautions for storage

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

In use: Following dilution in 0.9% Sodium Chloride Injection to a final concentration of 0.15 mg/ml, chemical and physical in-use stability has been demonstrated for up to 14 days at 4°C when protected from light.

From a microbiological point of view, however, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

10 mg/10 ml, 50 mg/50 ml and 100 mg/100 ml presentations in Type I amber glass vials and Onco-Tain vials. Packs contain a single vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Single use only. Discard any unused contents.

Refer to local cytotoxic handling guidelines.

Dilution prior to administration:

An appropriate volume of Cisplatin 1 mg/ml Concentrate for Solution for Infusion should be added to 2 litres of sterile 0.9% sodium chloride injection.
Dilution as recommended results in a clear, colourless solution with no visible particles.

Administration:

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Preparation (Guidelines):

1. Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

2. Operations such as dilution and transfer to syringes should be carried out only in the designated area.

3. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

4. Pregnant personnel are advised not to handle chemotherapeutic agents

Contamination:

(a) In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.

(b) In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and seal it.

Disposal:

Syringes, container, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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