SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cisplatin 1 mg/ml concentrate for solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
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

A clear colorless to pale yellow solution.

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.

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 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 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. Hydratation 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).

Method of administration
Cisplatin 1 mg/ml sterile concentrate is to be diluted before administration. For instructions for 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.

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 1litre.

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/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.

4.3 Contraindications

– Hypersensitivity to cisplatin or to any of the excipients listed in section 6.1.

Cisplatin may give allergic reactions in some patients. Use is contraindicated in those patients with a history of allergic reaction to cisplatin or other platinum containing compounds, or any component of the formulation. 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 should not breast feed (see section 4.6).

Concurrent administration of yellow fever vaccine is contraindicated.

4.4 Special warnings and precautions for use

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

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

The 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.

1. Nephrotoxicity

Cisplatin produces severe cumulative nephrotoxicity. Which may be potentiated by aminoglycoside antibiotics. The serum creatinine, plasma urea or creatinine clearance and magnesium, sodium potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Cisplatin should not be given more frequently than once every 3-4 weeks.

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/m^2/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (eg, mannitol).

2.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 vibration perception. A loss of motor function has also been reported. A neurologic examination must be carried out at regular intervals.

Neurotoxicity appears to be cumulative. Prior to each course, the absence of symptoms of peripheral neuropathy should be established.

3. Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin $50mg/m^2$, 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).

4. Allergic phenomena

Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin and have been alleviated by administration of adrenaline, steroids and antihistamines.

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

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

6. Carcinogenic potential
In humans, in rare cases the appearance of acute leukaemia has coincided with use of Cisplatin, which was in general associated with other leukaemogenic agents. Cisplatin is a bacterial mutagen and causes chromosome aberrations in cultures on animal cells. Carcinogenicity is possible but has not been demonstrated.
Cisplatin is teratogenetic and embryo toxic in mice.

7. 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.

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

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

Nausea and vomiting may be intense and require adequate antiemetic treatment. Close supervision must also be carried out with regard to ototoxicity, myelodepression and anaphylactic reactions (see section 4.8).

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 sodium per ml, equivalent to 38.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Nephrotoxic substances:
Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides or 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 renally 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.

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.

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.

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.

Anti-epileptics:
In patients receiving cisplatin and phenytoin, the serum level of phenytoin might be reduced. This is probably due to reduced absorption and/or increased metabolism. In these patients, one should monitor the levels of phenytoin in plasma, and adjust the dose accordingly.

4.6 Fertility, pregnancy and lactation

Pregnancy
Cisplatin may be toxic to the foetus when administered to a pregnant woman. Cisplatin should not be used during pregnancy unless the clinician considers the risk in an individual patient to be clinically justified.

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.

Breast-feeding
Cisplatin is excreted in breast milk. Patients treated with cisplatin must not breastfeed.

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

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.

Contraception in males and females
Male and female patients have to use effective contraception during and for at least 6 months after the treatment with cisplatin.

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 (>10%) of cisplatin were haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricemia) and fever.

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

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

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

System Organ Class	Frequency	MedDRA term
Infections and infestations	Not known	Infection[a]
	Common	Sepsis
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia
Neoplasm benign, malignant, and unspecified	Rare	Acute leukaemia
Immune system disorders	Uncommon	Anaphylactoid[b] reaction
Endocrine disorders	Not known	Blood amylase increased, inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Not known	Dehydration, hypokalaemia, hypophosphatemia, hyperuricemia, hypocalcaemia, tetany
	Uncommon	Hypomagnesaemia
	Very common	Hyponatraemia
Nervous system disorders	Not known	Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke

		ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
	Rare	Convulsion, neuropathy peripheral, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome
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	Not known	Cardiac disorder
	Common	Arrhythmia, bradycardia, tachycardia
	Rare	Myocardial infarction
	Very rare	Cardiac arrest
Vascular disorders	Common	Venous thromboembolism
	Not known	Thrombotic microangiopathy (haemolytic uremic syndrome), Raynaud's phenomenon
Gastrointestinal disorders	Not known	Vomiting, nausea, anorexia, hiccups, diarrhoea
	Rare	Stomatitis
Hepatobiliary disorders	Not known	Hepatic enzymes increased, blood bilirubin increased
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism
Skin and subcutaneous tissue disorders	Not known	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Not known	Muscle spasms
Renal and urinary disorders	Not known	Renal failure acute, renal failure[c] , renal tubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis

General disorders and administration site condition	Not known	Pyrexia (very common), asthenia, malaise, injection site extravasationd

a: Infectious complications have led to death in some patients.
b: Symptoms reported for anaphylactoid reaction such as facial edema (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 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

CAUTION IS ESSENTIAL IN ORDER TO PREVENT AN INADVERTANT 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, Platinum compounds,

ATC code: L01XA01

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, radiosensitising, and antimicrobial properties. Cisplatin does not appear to be cell-cycle specific.

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.

Distribution
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.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Do not bring in contact with aluminium.
Cisplatin reacts with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should be avoided. Cisplatin decomposes with solution in media with low chloride content; the chloride concentration should at least be equivalent to 0.45% of sodium chloride.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

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

6.3 Shelf life

Before opening
2 years

After dilution
Chemical and physical in-use stability after dilution with infusion fluids described in section 6.6, indicate that after dilution with recommended intravenous fluids, Cisplatin Injection remains stable for 14 days at 15 – 25 °C room temperature. The diluted solution should be protected from light.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 15 to 25 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

For 10 ml
10 ml type I amber glass vial with a flurotec rubber stopper, with an White colour flip off seal.

For 50 ml and 100 ml
50 ml type I amber glass vial with a flurotec rubber stopper, with an Purple colour flip off seal.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Preparation and handling of the product
Like with all anti-neoplastic products caution is needed with the processing of Cisplatin. Must be diluted before use. 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. See section “Disposal”.

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

- sodium chloride 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. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used. Only a clear solution, free from particles should be administered.

DO NOT bring in contact with injection material that contains aluminium DO NOT administer undiluted With respect to microbiological, chemical and physical stability with use of the undiluted solutions (see section 6.3).

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.

7 MARKETING AUTHORISATION HOLDER

Amarox Limited
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Harrow, HA1 2EN
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8 MARKETING AUTHORISATION NUMBER(S)

PL 49445/0179

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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