

1. NAME OF THE MEDICINAL PRODUCT

Cisplatin 0.5mg/ml Sterile Concentrate

10mg/ 20ml
25mg/ 50ml
50mg/ 100ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active constituent

Cisplatin	10mg	20ml water for injection
	25mg	50ml water for injection
	50mg	100ml water for injection

For excipients see section 6.1

3. PHARMACEUTICAL FORM

Sterile concentrate for solution for infusion. Clear, colourless to pale yellow, preservative free solution, free from visible particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cisplatin is indicated in metastatic, non-seminomatous germ cell carcinoma, advanced stage and refractory ovarian carcinoma, advanced stages and refractory bladder carcinoma and squamous cell carcinoma of head and neck.

Cisplatin is indicated in combination with other antineoplastic agents for the treatment of metastatic testicular tumours. The combination of Cisplatin, Vinblastine and Bleomycin is reported to be highly effective.

4.2 Posology and method of administration

Adults and children: Cisplatin should be administered by I.V. infusion over a 6-8 hour period. The recommended dose of Cisplatin in adults and children is 50 to 100 mg/m² as a single I.V. dose every 3 to 4 weeks, or 15 to 20mg/m² intravenously daily for 5 days every 3 to 4 weeks.

The dosage must be adjusted if the medicine is used together with other chemotherapy medication. A typical cisplatin dosage is 20mg/m² every 3 to 4 weeks, or more. The dosage should be reduced for patients with renal dysfunction or bone marrow suppression.

Interaction with aluminium:

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

1. *Pre-treatment Hydration:* Pre-treatment hydration is required to induce diuresis during (and after) Cisplatin administration. This hydration is achieved by giving 2 litres of either 0.9% Sodium Chloride or Dextrose 4% in one-fifth Normal Saline (0.18%) over a 2-hour period. During the last 30 minutes of the pre-treatment hydration or after the hydration, administer by side arm drip 37.5 g of Mannitol (i.e. 375 ml of mannitol 10% injection).
2. *Preparation of Cisplatin Infusion:* Cisplatin injection Solution 1mg/ML may be diluted in 2 litres of 0.9% Sodium Chloride Injection. Do not refrigerate solutions.
3. *Treatment:* Following prehydration, administer the Cisplatin infusion over 1 to 2 hours. It has been proposed that a longer infusion time of 6 to 8 hours may decrease the gastrointestinal and renal toxicities. The container should be covered to exclude light. Discard remaining contents after use.
4. *Post Treatment Hydration:* Continue I.V. hydration with the aim of administering another 2 litres of Sodium Chloride 0.9% Injection or Dextrose 4% in Sodium Chloride 0.18% Injection over a period of 6 to 12 hours.

4.3 Contraindications

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. Cisplatin nephrotoxicity is cumulative and may be irreversible. It is therefore, contraindicated in patients with renal impairment. The serum creatinine BUN and creatinine clearance should be measured prior to initiating therapy and monitored throughout treatment with Cisplatin. To reduce nephrotoxicity of Cisplatin treatment pre-treatment hydration procedures, together with maintenance of hydration and urinary output during the 24 hours following administration are necessary.

Cisplatin has been shown to be cumulatively ototoxic and should not be given to patients with hearing impairment. It is recommended that hearing function should be monitored prior to and during treatment with Cisplatin. Cisplatin is also contraindicated in myelosuppressed patients.

Cisplatin is contraindicated in pregnancy and breastfeeding.

Treatment with cisplatin is also contraindicated if a patient has a neuropathy secondary to its use.

4.4 Special warning and precautions for use

Not to be used undiluted.

Cisplatin must only be used by physicians experienced in cytotoxic chemotherapy.

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

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

In cases of extravasation:

- immediately end the infusion of cisplatin
- do not move the needle, aspirate the extravasate from the tissue, rinse with sodium chloride 0.9%.

Both male and female patients must use/take contraceptives to prevent conception and/or reproduction for at least six months after treatment with cisplatin. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. Since treatment with cisplatin may cause irreversible infertility, it is recommended that men who wish to become fathers in the future, ask for advice regarding cryo-conservation of their sperm prior to treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Cisplatin and antihypertensive therapy with Frusemide, Hydralazine, Diazoxide and Propranolol have been reported to cause nephrotoxicity.

Cisplatin may interact with aluminium. See dosage and administration.

Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control.

Concomitant administration of nephrotoxic agents (cephalosporins), or ototoxic agents (aminoglycosides) will potentiate the toxic effects of cisplatin on these organs.

During or after treatment with cisplatin, caution is advised with predominantly renally eliminated substances, including cytostatics such as bleomycin and methotrexate, since the renal secretion may be reduced.

A randomised study with patients suffering from advanced ovarian carcinoma showed adverse reactions to the therapy caused by simultaneous use of pyridoxine and hexamethylmelamine.

Simultaneous use of phosphamide causes increased protein secretion. The ototoxicity caused by cisplatin may be increased when it is used in combination with other medicines affecting hearing functions.

Except for patients receiving doses of cisplatin exceeding 60mg/m², whose urine secretion is less than 1000ml per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.

It may be required to adjust the dosage of allopurinol, colchicine, probenecid, or sulfinpyrazone if used together with cisplatin, since cisplatin causes an increase of uric acid content.

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

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

No living virus vaccination should be given within three months following the end of cisplatin treatment.

Chelating agents like penicillamine may diminish the effectiveness of cisplatin.

4.6 Pregnancy and lactation

Cisplatin is thought to cause serious birth defects when used during pregnancy. Its use in pregnancy is contraindicated.

Both male and female patients must use/take contraceptives to prevent conception and/or reproduction for at least six months after treatment with cisplatin. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. Since treatment with cisplatin may cause irreversible infertility, it is recommended that men, who wish to become fathers in the future, should ask for advice regarding cryo-conservation of their sperm prior to treatment. (See Section 4.4).

Breastfeeding during cisplatin therapy is contraindicated.

4.7 Effects on ability to drive and use machines

No or negligible influence.

4.8 Undesirable effects

1. *Nephrotoxicity*: Renal toxicity has been shown in 28-38% of patients treated with a single dose of Cisplatin 50 mg/m². Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must be restored before additional Cisplatin therapy is used. The renal impairment may be irreversible.
2. *Ototoxicity*: Ototoxicity has occurred in up to 31% of patients treated with a single dose of Cisplatin 50mg/m². Ototoxicity may be more severe in children and more

frequent and severe with repeated doses. The ototoxicity may be irreversible and usually occurs in the high frequency range. The patient should have audiometric testing before treatment starts.

3. *Haemotoxicity*: Myelosuppression is observed in about 30% of patients treated with Cisplatin. Leucopenia and thrombocytopenia are more pronounced at higher doses.
4. *Myelosuppression*: This may occur in patients treated with Cisplatin. The nadirs in circulating platelets and leucocytes generally occur between days 18-32 (range 7.3 to 45) with most patients recovering by day 39 (range 13 to 62). Leucopenia and thrombocytopenia are more pronounced at doses greater than 40 mg/m². Anaemia (decreases of greater than 2% haemoglobin) occurs at approximately the same frequency, but generally with a later onset than leucopenia and thrombocytopenia. Subsequent courses of Cisplatin should not be instituted until platelets are present at levels greater than 100.000/mm³ and white cells greater than 4.000/mm³. A high incidence of severe anaemia requiring transfusion of packed red cells has been observed in patients receiving combination chemotherapy including Cisplatin.
5. *Anaphylaxis*: 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.
6. *Hypomagnesaemia and Hypocalcaemia*: 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. Where both electrolytes are deficient, tetany may result. It does not appear to be dose related. Monitoring of electrolytes is necessary.
7. *Neurotoxicity and Seizures*: Peripheral neuropathy, postural hypotension and seizures may occur with Cisplatin administration. This appears to be common after Cisplatin administration. The development of clinically significant symptoms should generally contraindicate further Cisplatin usage.
8. *Ocular toxicity*: Loss of eyesight rarely occurs in the course of combination treatment with cisplatin. A papilloedema with visual defects has been incidentally noticed, but is reversible after ending the treatment. Only one case of unilateral retrobulbar neuritis with loss of vision sharpness has been reported after poly-chemotherapy followed by a cisplatin treatment.
9. *Gastro-intestinal toxicity*: Anorexia, taste loss, nausea, vomiting, stomach aches, and diarrhoea often occur between 1 and 4 hours after the use. These symptoms disappear for most patients after 24 hours. The liquid loss caused by vomiting and diarrhoea must be compensated. Less serious nausea and anorexia may continue to occur up to seven days after the treatment. Prophylactic administration of an anti-emetic may be effective. Oral mucositis rarely occurs.

10. Cardiac: Cardiac rhythm disorders including bradycardia and tachycardia rarely occur. Cardiac arrest has been reported in extremely rare cases after treatment with cisplatin combined with other cytostatic medicinal products.
11. Gingival: A metallic setting on the gums has been noticed.
12. Other: Local oedema and pain, erythema, skin ulceration and phlebitis may occur in the area of the injection after intravenous administration: Alopecia, dysfunctional spermatogenesis and ovulation, and painful gynaecomastia may occur.

The development of secondary non-lymphatic leukaemia has been linked to the use of cisplatin.

Independent descriptions link vascular disorders (cerebral or coronary ischaemia, infection of the peripheral blood circulation related to Raynaud's syndrome) with cisplatin including chemotherapy.

Carcinogenicity is theoretically possible, but not proven (based on cisplatin's active substances).

13. Immune system: Immunosuppression has been evidenced.
14. Serum electrolytes: The urea, serum creatinine, and uric acid levels may increase, while creatinine clearance may fall. Magnesium, calcium, phosphate, and potassium levels may decrease with symptomatic muscle cramps and rarely changes to the ECG as a result of renal damage.

4.9 Overdose

Overdosage can be expected to cause the toxic effects described above, but to an exaggerated degree. Adequate hydration and osmotic diuresis may help reduce the toxicity of Cisplatin if administered promptly following overdosage.

Convulsions may be treated with appropriate anti-convulsants. 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.

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

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

There is a good uptake of Cisplatin by the kidneys, liver, intestine and testicles. 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.

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. The 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. Cisplatin shows non-linear pharmacokinetics.

5.3 Preclinical safety data

Chronic toxicity: Chronic toxicity models indicate kidney damage, bone marrow depression, gastro-intestinal disorders and ototoxicity.

Mutagenicity and carcinogenicity: Cisplatin is mutagenic in numerous in vitro and in vivo tests (chromosome defects in animal cells, tissue cultures and bacterial test systems). Long term studies of cisplatin on mice and rats evidenced the carcinogenic effects.

Reproductive toxicity:

Fertility: Gonadal suppression resulting in amenorrhoea or azospermia may be irreversible and cause infertility.

Pregnancy: Cisplatin is embryotoxic for mice and rats, and defects have been reported for both species. Cisplatin was found in the milk of milk producing animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Hydrochloric acid
Water for injection

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

This medicinal product must not be mixed with other medicinal products. Cisplatin should not come into contact with aluminium (needles, syringes, catheters).

6.3 Shelf life

24 months. Twenty four hour chemical stability at 4°C and 25°C with 0.9% sodium chloride solution in a final concentration of 0.1 mg/ml Cisplatin has been demonstrated.

From a microbiological point of view, 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 to 8°C. The diluted solution should be protected from light.

6.4 Special precautions for storage

Do not store above 25°C. keep container in the outer carton. Do not refrigerate or freeze. Protect diluted solution from light.

6.5 Nature and contents of container

Brown coloured Type I glass with bromobutyl stopper
20ml, 50ml & 100ml vial

6.6 Instructions for use and handling

See Sections 4.2, 4.3, and 4.4.

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd
NLA Tower
Croydon
CRO OXT
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 12762/0089

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/04/2009

10. DATE OF REVISION OF THE TEXT

02/04/2009