Package leaflet: Information for the user

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

Cisplatin concentrate for solution for infusion is given only by healthcare personnel, who can reply to any questions, which you may have after reading this package leaflet.

1. What Cisplatin is and what it is used for

Cisplatin forms part of a group of medicines called cytostatics, which are used in the treatment of cancer. Cisplatin can be used alone but more commonly Cisplatin is used in combination with other cytostatics.

Cisplatin is used to treat cancers of the testis, ovary, urinary bladder, head and neck, and lung.
Cisplatin is used to treat cervical cancer in combination with radiotherapy.
Your doctor will be able to provide you with more information.

2. What you need to know before you use Cisplatin

Do not use Cisplatin:
- if you are allergic to cisplatin or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to any other medicine that contains platinum compounds
- if you have kidney problems (renal dysfunction)
- if you suffer from dehydration
- if you suffer from severe suppression of bone marrow functionality, symptoms may be extreme tiredness, easy bruising or bleeding, occurrence of infections
- if your hearing is impaired
- if you suffer from nervous disorders caused by cisplatin
- if you are breast-feeding
- combined with live vaccines, including yellow fever vaccine
- combined with phenytoin in prophylactic use (see “Use of Cisplatin with other medicines” below).

Warnings and precautions
- Your doctor will carry out tests in order to determine the levels of calcium, sodium, potassium and magnesium in your blood, as well as to check your blood picture and your liver and kidney functionality and neurological function.
- Cisplatin should only be administered under the strict supervision of a specialist doctor experienced in administrating chemotherapy.
- Your hearing will be tested prior to each treatment with Cisplatin.

Take special care with Cisplatin:
- if you suffer from a nervous disorder not caused by Cisplatin.
- if you suffer from an infection. Please consult your doctor.
- if you intend to have children (see Pregnancy, breast-feeding and fertility).

With spillage of cisplatin the contaminated skin must immediately be washed with water and soap. If cisplatin is injected outside the blood vessels the administration must be stopped immediately. Infiltration of cisplatin in the skin can result in tissue damage (cellulitis, fibrosis and necrosis).

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Other medicines and Cisplatin
Tell your doctor if you are taking, have recently taken or might take any other medicines

- Simultaneous use of medicines that inhibit the **bone marrow** function or radiation can potentiate the adverse effects of cisplatin on the bone marrow. Your hearing will be tested prior to each treatment with Cisplatin.
- Cisplatin toxicity may increase when administered simultaneously with other **cytostatics** (medicine for cancer treatment), such as bleomycin and methotrexate.
- Agents to treat high blood pressure (**antihypertensives** containing furosemide, hydralazine, diazoxide, and propanolol) may increase the toxic effect of Cisplatin on kidneys.
- Cisplatin toxicity may severely affect the kidneys when administered simultaneously with agents that may cause side effects in the kidneys, such as those for the prevention/treatment of certain infections (**antibiotics**: cephalosporins, aminoglycosides, and/or amphotericin B) and **contrast agents**.
- Cisplatin toxicity may affect hearing faculties when administered simultaneously with agents that may have a side effect on hearing faculties, such as **aminoglycosides**.
- If you use agents to treat **gout** during your treatment with cisplatin, then the dosage of such agents may need to be adjusted (e.g. allopurinol, colchicine, probenecid and/or sulfinpyrazone).
- Administration of drugs that elevate your rate of bodily urine excretion (**loop diuretics**) combined with cisplatin (cisplatin dose: more than 60mg/m², urine secretion: less than 1000 ml per 24 hours) may result in toxic effects on kidneys and hearing.
- The first signs of hearing damage (dizziness and/or tinnitus) may remain hidden when – during your treatment with cisplatin – you are also being administered agents to treat hypersensitivity (**antihistamines**, such as buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes and/or trimethobenzamides).
- Cisplatin given in combination with **ifosphamide** may result in hearing impairment.
- The effects of treatment with cisplatin can be reduced through simultaneous administration of **pyridoxine** and **hexamethylmelamine**
- Cisplatin given in combination with **bleomycin** and **vinblastin** may result in paleness or blue coloration of the fingers and/or toes (Raynaud`s phenomenon).
- Administration of cisplatin prior to treatment with **paclitaxel** or in combination with **docetaxel** may result in severe nerve damage.
- The combined use of cisplatin with **bleomycin** and **etoposide** may decrease lithium levels in the blood. Therefore, lithium levels should be checked on a regular basis.
- Cisplatin reduces the effects of **phenytoin** on the treatment of epilepsy.
- **Penicillamine** may reduce the effectiveness of Cisplatin.
- Cisplatin may have an adverse impact on the effectiveness of agents preventing coagulation (**anticoagulants**). Therefore, coagulation should be checked more often during combined use.

- Cisplatin and **ciclosporin** may result in suppression of the immune system with the risk of increased production of white blood cells (lymphocytes).
- You should not receive any **vaccinations** containing live viruses within three months after the end of treatment with cisplatin.
- When undergoing treatment with cisplatin, you should not receive **yellow fever vaccinations** (also see "Do not take Cisplatin").

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you begin to use, or are administered Cisplatin.

Cisplatin must not be used during **pregnancy** unless clearly indicated by your doctor. You must use effective contraception during and at least 6 months after treatment with Cisplatin.

You must not breast-feed while you are treated with Cisplatin.

Male patients treated with Cisplatin are advised not to father a child during treatment and for up to 6 months after treatment. Further, men are advised to seek counselling on sperm preservation before starting treatment.

Driving and using machines
Cisplatin may cause side effects such as feeling sleepy and/or vomiting. If you suffer from either of these conditions, then you should not operate any machines that require your full attention.

Cisplatin Contains sodium
Cisplatin contains 3.5 mg sodium per ml. This should be considered if you have to keep a low sodium diet.

3. How to use Cisplatin

Dosage and method of administration
Cisplatin should only be given by a specialist in cancer treatment.
The concentrate is diluted with a sodium chloride solution or a solution that contains glucose.

Cisplatin is only given by injection into a vein (an intravenous infusion).
Cisplatin should not come into contact with any materials that contain aluminium. The recommended dosage of Cisplatin depends on your well-being, the anticipated effects of the treatment, and whether or not cisplatin is given on its own (monotherapy) or in combination with other agents (combination chemotherapy).

Cisplatin (monotherapy):
The following dosages are recommended:
- A *single* dosage of 50 to 120 mg/m² body surface, every 3 to 4 weeks.
- 15 to 20 mg/m² per day over a 5-day period, every 3 to 4 weeks.

Cisplatin in combination with other chemotherapeutical agents (combination chemotherapy):
20 mg/m² or more, once every 3 to 4 weeks.

For treatment of cervical cancer cisplatin is used in combination with radiotherapy.
A typical dose is 40 mg/m2 weekly for 6 weeks.

In order to avoid, or reduce, kidney problems, you are advised to drink copious amounts of water for a period of 24 hours following treatment with Cisplatin.

If you receive more Cisplatin than you should

Your doctor will ensure that the correct dose for your condition is given. In case of overdose, you may experience increased side effects. Your doctor may give you symptomatic treatment for these side effects. If you think you received too much Cisplatin, immediately contact your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you experience any side effect it is important that you inform your doctor before your next treatment.

Tell your doctor immediately, if you notice any of the following:
- severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint;
- severe chest pains possibly radiating to the jaw or arm with sweating, breathlessness and nausea (heart attack);
- persistent or severe diarrhoea or vomiting;
- sore lips or mouth ulcer (stomatitis/mucositis) ;
- unexplained respiratory symptoms such as non-productive cough, difficulty in breathing or crackles;
- numbness or tingling in your fingers or toes ;
- extreme tiredness;
- abnormal bruising or bleeding;
- signs of infection, such as sore throat and high temperature;
- sensation of discomfort close to or at the injection site during the infusion.

The following side effects may occur:

Very common (*may affect more than 1 in 10 people*)
- decrease in bone marrow function (which can affect the production of blood cells)
- decrease in white blood cells, which makes infections more likely (leukopenia)
- decrease in blood platelets, which increases the risk of bruising and bleeding (thrombocytopenia)
- reduction of red blood cells which can cause weakness and your skin to look pale (anaemia)
- reduced level of sodium in the blood
- high temperature
- problems with your kidneys or urine

Common *(may affect up to1 in 10 people*)
- fast, irregular or slow heart beats
- sepsis (blood poisoning)
- inflammation of a vein (phlebitis)
- difficulty breathing (dyspnoea)
- pneumonia
- respiratory failure
- redness and inflammation of the skin (erythema, skin ulcer) in the area of the injection
- swelling (oedema)
- pain at the area of injection
- damage to the nervous system (neurotoxicity)

Uncommon (*may affect up to 1 in 100 people*)
- severe allergic reaction (see above)
- hearing loss (ototoxicity)
- reduced level of magnesium in the blood
- abnormal sperm production and ovulation

- painful breast growth in men (gynaecomastia)

Rare *(may affect up to 1 in 1,000 people*)
- increased risk of acute leukaemia
- convulsions
- fainting, headache, confusion and loss of vision
- loss of certain types of brain function, including brain dysfunction characterised by spasms and reduced level of consciousness
- heart attack
- inflammation of mucous membranes of the mouth (stomatitis).
- peripheral neuropathy of the sensory nerves, characterised by tickling, itching or tingling without cause and sometimes with loss of taste, touch, sight, sudden shooting pains from the neck through the back and into the legs when bending forward.
- a problem with the way the body fights diseases (immunosuppression)
- excessive cholesterol levels in the blood
- inflammation of the eye nerve combined with pain and reduced nerve function (optic neuritis)
- eye movement dysfunction
- coronary artery disease
- high blood pressure
- decreased level of blood albumin

Very rare *(may affect up to 1 in 10,000 people)*
- heart arrest
- seizures

Not known (*frequency cannot be estimated from the available data*)
- signs of infection such as fever or sore throat
- haemolytic anaemia
- inappropriate release of vasopressin hormone (ADH) which may lead to low sodium in the blood and water retention
- blood amylase (enzyme) increased
- dehydration
- reduced level of calcium, phosphate, potassium in the blood
- high level of uric acid in the blood
- muscle cramping
- spinal disease which may cause a sensation of electric shocks passing into your limbs
- brain dysfunction (confusion, slurred speech, sometimes blindness, memory loss, and paralysis)
- stroke
- loss of taste
- problems with your eyesight (blurred vision, odd colours, loss of vision or eye pain)
- ringing in the ears or deafness
- heart problems
- unusually cold or white hands and feet
- tingling, numbness or tremor in your hands, feet, arms or legs
- blood clot in the lung
- persistent headache
- feeling or being sick
- loss of appetite, anorexia
- hiccups
- diarrhoea
- liver enzymes increased, bilirubin increased
- hair loss
- rash
- extreme tiredness/weakness
- swelling or soreness where the injection was given
- cramps or spasms
- burning or prickling sensation

- unexpected bruising or bleeding
- haemolytic uraemic syndrome which may cause changes to the kidneys and blood

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 676497; Fax: +353 1 6762517. Website: www.hpra.ie ; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cisplatin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial and the outer carton after 'exp'. The expiry date refers to the last day of that month.

Keep the vial in the outer carton in order to protect from light. Do not store above 25°C.

Do not refrigerate or freeze.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 15-25°C
From a microbiological point of view, the product should be used immediately.

6. Contents of the pack and other information

What Cisplatin contains
The active substance is cisplatin.
1 ml of concentrate for solution for infusion contains 1 mg of cisplatin.
One vial of 10 ml concentrate for solution for infusion contains 10 mg cisplatin. One vial of 50 ml concentrate for solution for infusion contains 50 mg cisplatin.

The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment) and water for injections.

What Cisplatin looks like and contents of the pack
Cisplatin is a clear, slightly yellow concentrate for solution for infusion free from visible particles in glass injection vials.

Packaging with 1 vial of 10 ml of concentrate, the vial containing 10 mg cisplatin. Packaging with 1 vial of 50 ml of concentrate, the vial containing 50 mg cisplatin.

Vial will be packed with or without a protective plastic overwrap

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Caduceus Pharma Limited

2 Martin House
179-181 North End Road
London W14 9NL
United Kingdom

Manufacturer
S.C. Sindan-Pharma S.R.L.
11 Ion Mihalache Blvd,
011171 Bucharest
Romania

This medicinal product is authorised in the Member States of the EEA under the following names:

AT Cisplatin Caduceus
DE Cisplatin Caduceus
HU Cisplatin Caduceus
IE Cisplatin 1 mg/ml Concentrate for Solution for Infusion
IT Cisplatino Caduceus
PL Cisplatin Caduceus
UK Cisplatin 1 mg/ml Concentrate for Solution for Infusion

This leaflet was last revised in February 2017.

The following information is intended for medical or healthcare professionals only:

Preparation and handling of the product

For single use only.
Refer to local cytotoxic guidelines.

Like with all anti-neoplastic products caution is needed with the processing of cisplatin. Dilution should take place under aseptic conditions in a safety box, by trained personnel in an area specifically intended for this, and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses. Precautions should be taken to avoid contact with the skin and mucous membranes. If skin contact did occur anyway, the skin should be washed with soap and water immediately. With skin contact tingling, burns and redness have been observed. In case of contact with the mucous membranes they should be copiously rinsed with water. After inhalation dyspnoea, pain in the chest, throat irritation and nausea have been reported.

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

Pregnant women must avoid contact with cytostatic drugs.

Bodily waste matter and vomit should be disposed with care.

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

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

Preparation of the intravenous administration

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 9mg/ml (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 (final concentrations)
- sodium chloride 0.45%, glucose 2.5% and 1.875% mannitol for injection (final concentrations).

Always look at the injection before use. Only a clear solution, free from particles should be administered.

DO NOT bring in contact with injection material that contains aluminium.

DO NOT administer undiluted.
With respect to chemical and physical stability with use of the undiluted solutions, see section ”Special precautions for storage – undiluted solution.”

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.

Incompatibilities
Do not bring in contact with aluminium. Cisplatin reacts with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should be avoided.

Cisplatin decomposes with solution in media with low chloride content; the chloride concentration should at least be equivalent to 0. 45% of sodium chloride.

Antioxidants (such as sodium metabisulphite), bicarbonates (sodium bicarbonate), sulphates, fluorouracil and paclitaxel may inactivate cisplatin in infusion systems.
This medicinal product must not be mixed with other medicinal products except those mentioned in above mentioned section “Preparation of the intravenous administration”.

Special precautions for storage

Medicinal product as packaged for sale:
Concentrate for solution for infusion 1 mg/ml

Undiluted solution: Do not store above 25°C. Do not refrigerate or freeze. Keep the vial in the outer carton in order to protect from light. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used.

Diluted solution:
Do not store diluted solutions in the refrigerator or freezer.

After dilution in infusion fluids mentioned above:
Chemical and physical in-use stability has been demonstrated for 24 hours at 15-25°C.
From a microbiological point of view, the product should always be used immediately.