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 using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cisplatin is and what it is used for
2. What you need to know before you use Cisplatin
3. How to use Cisplatin
4. Possible side effects
5. How to store Cisplatin
6. Contents of the pack and other information

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.

What it is used for

Cisplatin can destroy cells in your body that may cause certain types of cancer (tumour of testis, tumour of ovary, tumour of the bladder, head and neck epithelial tumour, lung cancer and for cervical cancer in combination with radiotherapy).

2. WHAT YOU NEED TO KNOW BEFORE YOU USE CISPLATIN

Do not take Cisplatin if:
- you are allergic to cisplatin or to any of the other ingredients of this medicine (listed in section 6)
- you are allergic (hypersensitive) to any other medicine that contains platina compounds
- you have kidney problems (renal dysfunction)
- you suffer from dehydration
- you suffer from severe suppression of bone marrow functionality, symptoms may be: extreme tiredness, easy bruising or bleeding, occurrence of infections
- your hearing is impaired
- you suffer from nervous disorders caused by cisplatin
- you are breast-feeding
- combined with live vaccines, including yellow fever vaccine
- combined with phenytoin in prophylactic use (see "Other medicines and Cisplatin" 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.
- If you suffer from a nervous disorder not caused by Cisplatin.
- If you have had radiation therapy to your head
- If you suffer from an infection. Please consult your doctor.
- If you intend to have children (see Pregnancy, breast-feeding and fertility)

Tell your doctor if the above applies to you before this medicine is used.

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

Please note that these statements may also apply to products used some time ago or at some time in the future. Tell your doctor or pharmacist if you are taking, or have recently taken, or might take any other medicine.
- Simultaneous use of medicines that inhibit the **bone marrow** function or radiation can potentiate the adverse effects of Cisplatin on the bone marrow.
- 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 propranolol) 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 **vinblastine** 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** and *other so called chelating agents* may reduce the effectiveness of Cisplatin.
- Cisplatin may have an adverse impact on the effectivity of agents preventing coagulation (**anticoagulants**). Therefore, coagulation should be checked more often during combined use.
- Concomitant use of cisplatin with **ciclosporin** can weaken 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 for advice before using this medicine. 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.

Breast-feeding

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

Fertility

Male patients treated with cisplatin are advised not to father a child during treatment and for up to 6 months after treatment. Further, male patients should seek advice regarding cryoconservation of sperm prior to treatment with Cisplatin.

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 50mg/50ml contains 177 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 8.9% of the recommended maximum daily dietary intake of sodium for an adult.

Cisplatin 100mg/100ml contains 354 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 17.7% of the recommended maximum daily dietary intake of sodium for an adult.

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.

Cisplatin is only given by injection into a vein (an intravenous infusion).

Supportive equipment should be available to control anaphylactic reactions.

Cisplatin should not come into contact with any materials that contain aluminium.

The recommended dosage of cisplatin depends on your well-being, the anticipated effect 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 recommended dose is:
- 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 use 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 or nurse.

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:
- persistent or severe diarrhoea or vomiting
- stomatitis/mucositis (sore lips or mouth ulcer)
- swelling of the face, lips mouth or throat
- unexplained respiratory symptoms such as non-productive cough, difficulty in breathing or crackles
- difficulty in swallowing
- 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.
- severe pain or swelling in either of your legs, chest pain, or difficulty breathing (possibly indicating harmful blood clots in a vein) (common: may affect up to 1 in every 10 people)

The following side effects may occur:

Very common: may affect more than 1 in 10 people
- reduction in the number of white blood cells which makes infections more likely (leukopenia)
- reduction in blood platelets which increases the risk of bruising and bleeding (thrombocytopenia)
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- renal dysfunction such as failure to produce urine (anuria)
- urine poisoning of the blood (uraemia)
- reduced level of electrolytes (sodium)
- hyperuricaemia (high level of uric acid in the blood).

Common: may affect up to 1 in 10 people
- blood-poisoning (sepsis)
- damage to the nervous system (neurotoxicity)
- arrhythmia, including reduced heartbeat (bradycardia), accelerated heartbeat (tachycardia)
- inflammation of a vein (phlebitis)
- difficulty in breathing (dyspnoea), inflammation of the lungs (pneumonia) and 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
- vertigo.

Uncommon: may affect up to 1 in 100 people
- severe hypersensitivity (anaphylactic) reactions including rash, eczema with severe itching and lump formation (urticaria), redness and inflammation of the skin (erythema) or itching (pruritus), anaphylactoid reactions with symptoms such as swelling of the face and fever, low blood pressure (hypotension), accelerated heartbeat (tachycardia), breathing difficulties (dyspnoea), distress as a result of muscle cramps in the airways (bronchospasms)
- reduced level of electrolytes (magnesium)
- loss of hearing (ototoxicity)
- dysfunctional spermatogenesis (abnormal sperm production) and ovulation, and painful breast growth in men (gynaecomastia)

The following information is intended for medical or healthcare professionals only

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Further to the information included in section 3, practical information on the preparation/handling of the medicinal product is provided here.

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.

Shelf life after opening:

Chemical and physical stability was demonstrated for 56 days at 20 - 25 °C, exposed or protected from light. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Shelf-life after dilution:

Chemical and physical in-use stability after dilution with infusion fluids described in section 6.6 of the SPC, indicate that after dilution with recommended intravenous fluids, Cisplatin remains stable for 48 hours at 15 - 25 °C room temperature under protection from light.
The diluted solution should be protected from light.
Do not store diluted solutions in the refrigerator or freezer.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and dilution should taken place in controlled and validated aseptic conditions.

Preparation of the intravenous administration:

Take the quantity of the solution that is needed from the bottle and dilute with 1 or 2 liters of the following solutions:
- sodium chloride 0.9%,
- Mixture of sodium chloride 0.9% / glucose 5 (1:1),

Rare: may affect up to 1 in 1,000 people
- increases risk of leukaemia (acute leukaemia)
- suppression of immune system (immunosuppression)
- high levels of cholesterol in the blood (hypercholestrerolemia)
- peripheral neuropathy of the sensory nerves (bilateral, sensory neuropathy), characterised by tickling, itching or tingling without cause and sometimes characterised by a loss of taste, touch, sight, as well as brain dysfunction (confusion, slurred speech, sometimes blindness, memory loss, and paralysis); sudden shooting pains from the neck through the back into the legs when bending forwards, spinal disease, convulsions, loss of certain types of brain function, including brain dysfunction characterised by spasms and reduced levels of consciousness (encephalopathy), as well as closure of the carotid artery
- inflammation of the eye nerve combined with pain and reduced nerve function (optic neuritis), eye movement dysfunction
- coronary artery disease, heart attack
- increased blood pressure levels (hypertension)
- inflammation of mucous membranes of the mouth (stomatitis)
- reduced albumin (protein) levels in the blood.

Very rare: may affect up to 1 in 10,000 people
- attacks (seizures)
- increased blood iron.

Not known: frequency cannot be estimated from the available data
- increased blood amylase (enzyme) levels
- reduced level of electrolytes (magnesium, calcium, sodium, phosphate, potassium) in the blood with muscle cramping and/or changes in an electrocardiogram (ECG), dehydration, involuntary contraction of muscles (tetany).
- stroke (cerebrovascular accident)
- loss of sight (blindness), difficulties in colour perception, blurred vision, swelling (papilloedema)
- deafness, tinnitus
- cardiac disorder
- blood flow dysfunction, e. g. in the brain, but also in the fingers and toes (Raynaud´s syndrome)
- pulmonary embolism (blood clot in the lung)
- loss of appetite (anorexia), nausea, vomiting, diarrhoea,
- hiccups
- loss of hair (alopecia), rash
- fever, weakness (asthenia), malaise
- stroke (cerebrovascular accident).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. 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.

Expiry
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. Do not use this medicine if you notice visible signs of deterioration.

Storage
Do not store above 25°C. Do not refrigerate or freeze. Keep container in the outer carton in order to protect from light.

Prepared infusions should be used immediately, however, if this is not possible, they can be stored for up to 48 hours at 15 - 25 °C room temperature under protection from light provided they have been prepared in a way to exclude microbial contamination. The prepared infusions should not be refrigerated.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Cisplatin contains
The active substance is cisplatin.
Each milliliter (ml) of solution contains 1 milligram (mg) of cisplatin.

The other ingredients are sodium chloride, hydrochloric acid 37%, sodium hydroxide and water for injections.

What Cisplatin looks like and contents of the pack
Cisplatin is a clear, colourless to pale yellow concentrate for solution for infusion packaged in an amber glass vial of 50 ml or 100 ml.

The vials are packed in carton boxes containing 1 vial.

Marketing authorisation holder and Manufacturer
Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó 8, 8A e 8B
2705-906 Terrugem SNT, Portugal

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(resulting final concentration: sodium chloride 0.45%, glucose 2.5%)
- sodium chloride 0.9% and 1.875% mannitol
- sodium chloride 0.45%, glucose 2.5% and 1.875% mannitol

Compatibility with the above solutions has been demonstrated at concentration of 0.1 and 0.22 mg/ml. DO NOT bring in contact with injection material that contains aluminium.

DO NOT administer undiluted.

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 reconstitution, 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.