Package leaflet: Information for the user

Cisplatin 1 mg/ml

concentrate for solution for infusion

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 any further questions, ask your doctor, pharmacist or nurse.
- 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

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 is it used for?

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 take Cisplatin if:

- if you are allergic (hypersensitive) to cisplatin or other platinum compounds or any of the other ingredients of this medicine (listed in section 6)
- 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 yellow vaccine and phenytoin (see "Other medicines and Cisplatin " below).

Warnings and precautions

Talk to your doctor or pharmacist or nurse before using cisplatin.

- 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 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

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, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- 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 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 60 mg/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 flue 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 efficacy 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

Pregnancy

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.

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.
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 taking this medicine.

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

This medicinal product contains less than 1 mmol sodium (9 mg) per ml, i.e. essentially 'sodium- free'. This should be considered if you have to keep a low sodium diet.

3. How to use Cisplatin

Dosage and method of administration

Cisplatin must only be given by a specialist in cancer treatment. The concentrate is diluted with a sodium chloride 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 believe you have received 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 product, 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:

- 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.

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).

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.

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 and ovulation, and painful breast growth in men (gynaecomastia)

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)

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

The following information is intended for healthcare professionals only:

Preparation and handling of the product

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 9 mg/ml (0.9%);
- mixture of sodium chloride 9 mg/ml (0.9%)/ glucose 50 mg/ml (5%) (1:1), (resulting final concentrations: sodium chloride 4.5 mg/ml (0. 45%), glucose 25 mg/ml (2. 5%));

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 "How to store Cisplatin ."

<u>Preparation of the intravenous solution-Warning</u>

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.

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.

- loss of appetite (anorexia), nausea, vomiting, diarrhoea, hiccups
- loss of hair (alopecia), rash
- fever, weakness (asthenia), malaise
- stroke (cerebrovascular accident).

Reporting of side effects

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.

For UK - You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

For Ireland - Via;
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
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 label and carton after "Exp. The expiry date refers to the last day of that month.

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

After dilution:

Chemical and physical in-use stability has been demonstrated for 8 hours at 15-25°C in ambient light and for 14 days at 15-25°C under protection from light.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in use storage and times conditions are the responsibility of user. The diluted solution should be protected from light. Do not store diluted solutions in the refrigerator or freezer.

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.

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 of cisplatin.
One vial of 20 ml concentrate for solution for infusion contains 20 mg of cisplatin.
One vial of 50 ml concentrate for solution for infusion contains 50 mg of cisplatin.
One vial of 100 ml concentrate for solution for infusion contains 100 mg of cisplatin.

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

What Cisplatin look s like and contents of the pack

This medicinal product is a concentrate for solution for infusion.

Cisplatin is a clear, colourless to pale yellow concentrate for solution for infusion free from visible particles in glass injection vials.

10 ml vial: 20 ml moulded amber coloured Type I vial with chlorobutyl rubber stopper and sealed with green flip-off aluminium seal.

20 ml vial: 20 ml moulded amber coloured Type I vial with chlorobutyl rubber stopper and sealed with red flip-off aluminium seal.

50 ml vial: 50 ml moulded amber coloured Type I vial with chlorobutyl rubber stopper and sealed with yellow flip-off aluminium seal.

100 ml vial: 100 ml moulded amber coloured Type I vial with chlorobutyl rubber stopper and sealed with purple flip-off aluminium seal.

Pack Sizes:

1 x 10 ml vial
1 x 20 ml vial
1 x 50 ml vial
1 x 100 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

For UK:

Fresenius Kabi Oncology Plc
Lion Court, Farnham Road Bordon, Hampshire,
GU35 0NF United Kingdom

For IRL :

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

Manufacturer:

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire,
GU35 0NF United Kingdom

Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg
Germany

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

Austria	Cisplatin Kabi 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Cisplatine Fresenius Kabi 1 mg/ml, concentraat voor oplossing voor infusie
Cyprus	Cisplatin/Kabi 1 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Czech Republic	Cisplatin Kabi 1 mg/ml
Germany	Cisplatin Kabi 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Denmark	Cisplatin Fresenius Kabi
Estonia	Cisplatin Kabi 1 mg/ml
Greece	Cisplatin/Kabi 1 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Spain	Cisplatino Kabi 1mg/ml concentrado para solución para perfusión EFG
France	Cisplatine Kabi 1 mg/ml, solution à diluer pour perfusion
Hungary	Cisplatin Kabi 1 mg/ml koncentrátum oldatos infúzióhoz
Ireland	Cisplatin 1 mg/ml concentrate for solution for infusion
Italy	Cisplatino Kabi
Latvia	Cisplatin Kabi 1 mg/ml koncentrāts infūziju šķīduma pagatavošanai
Lithuania	Cisplatin Kabi 1 mg/ml koncentratas infuziniam tirpalui
Luxemburg	Cisplatin Kabi 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Malta	Cisplatin 1 mg/ml concentrate for solution for infusion
The Netherlands	Cisplatine Fresenius Kabi 1 mg/ml, concentraat voor oplossing voor infusie
Norway	Cisplatin Fresenius Kabi
Poland	Cisplatin Kabi
Portugal	Cisplatina Kabi
Romania	Cisplatina Kabi 1 mg/ml concentrat pentru soluție perfuzabilă
Slovak Republic	Cisplatin Kabi 1 mg/ml
Slovenia	Cisplatin Kabi 1 mg/ml koncentrat za raztopino za infundiranje
United Kingdom	Cisplatin 1 mg/ml concentrate for solution for infusion

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