PACKAGE LEAFLET: INFORMATION FOR THE USER

Cisplatin 'Ebewe' 1 mg/ml, Concentrate for solution for infusion

cisplatin

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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 can destroy cells in your body that may cause certain types of cancer (tumour of testis, tumour of ovary, head and neck epithelial tumour (tumour affecting the outer tissue layer of the skin), tumour in the lung).
Your doctor will be able to provide you with more information.

2. BEFORE YOU TAKE CISPLATIN

Do not take Cisplatin if:
- you are allergic (hypersensitive) to cisplatin or to any of the other ingredients of Cisplatin
- you are allergic (hypersensitive) to any other medicine that contains platin
- you have kidney problems (renal dysfunction)
- you suffer from dehydration
- you suffer from severe suppression of bone marrow functionality

- your hearing impaired
- you suffer from nervous disorders caused by cisplatin
- you are pregnant or breastfeeding
- combined with yellow vaccine and phenytoin (see "Use of Cisplatin with other medicines" below).

Take special care with 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.
- 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 fathering children).

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

Taking other medicines

Please note that these statements may also apply to products used some time ago or at some time in the future.

Please inform your doctor or pharmacist if you are taking, of have recently taken, any other medicine – even those not prescribed.

- Cisplatin toxicticity 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, hydraalzine, 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 whith 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 needs to be adjusted (e.g. allopurinol, cholchicine, 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 flue coloration of the fingers and/or toes (Raynaud`s phenomenon).
- Administration of cisplatin for 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 effectivity 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 decreased production of white blood cells (lymphocytes).
- You should not receive any vaccinations containing live viruses within three months 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 fathering children
Ask your doctor or pharmacist for advice before you begin to use, or are administered, Cisplatin.

Cisplatin must not be used during **pregnancy**.
YOU MUST USE EFFECTIVE CONTRACEPTION DURING AND AT LEAST 6 MONTHS AFTER TREATMENT WITH CISPLATIN.

Cisplatin must not be used while **breast-feeding**.

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 counseling on sperm preservation before starting treatment.

Driving and using machines
Cisplatin may make you feel sleepy and/or vomiting. If you suffer from either of these conditions, then you should not operate any machines that require your full attention.

Important information about some of the ingredients of Cisplatin
Cisplatin contains 3.5 mg sodium per ml. This should be considered if you have to keep low sodium diet.

3. HOW CISPLATIN 1 mg/ml IS GIVEN

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 sodium chloride solution that contains glucose, or a sodium chloride solution that contains mannitol.

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 1 mg/ml (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 1 mg/ml in combination
with other chemotherapeutical agents (combination chemotherapy):
- The typical dosage is 20 mg/m² or more, every 3 to 4 weeks
- In the treatment of tumours in the lung the typical dosage is 80 mg/m²

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 have any further questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cisplatin can have side effects.
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 diarrhea 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.

Side effects may appear *very common* (in more than 1 in 10 patients);
common (in more than 1 in 100, but less than 1 in 10 patients);
uncommon (in more than 1 in 1,000, but less than 1 in 100 patients);
rarely (in more than 1 in 10,000, but less than 1 in 1,000 patients);
very rarely (in less than 1 in 10,000 patients);

The following side effects may occur:

Very common
Blood and lymphatic system: 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), as well as reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness (anaemia).
Hearing and balance function: loss of hearing combined with tinnitus.
Gastrointestinal tract: loss of appetite (anorexia), nausea, vomiting, diarrhoea.
Kidneys and urinary tracts: renal dysfunction, such as failure to produce urine (anuria) and urine poisoning of the blood (uraemia), and excessive urine acid levels (hyperuricaemia) in the blood (e.g. gout).
General symptoms: fever.

Common
Infections: Infections and blood-poisoning (sepsis).
Blood and lymphatic system: reduction in the number of white blood cells (leukopenia; approximately 14 days after use), reduction in blood platelets (thrombocytopenia; approximately 21 days after use) and reduction in red blood cells (later onset than leukopenia and thrombocytopenia).
Nervous system: peripheral neuropathy 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.
Hearing and balance function: deafness and dizziness.
Heart: arrhythmia, including reduced heartbeat (bradycardia), accelerated heartbeat (tachycardia).
Blood vessels: inflammation of a vein (phlebitis).
Respiratory disorders: difficulty of breathing (dyspnoea), inflammation of the lungs (pneumonia) and respiratory failure.
Liver and bile: liver dysfunction.
Skin: redness and inflammation of the skin (erythema, skin ulcer) in the area of the injection.

General symptoms: swelling (oedema), pain.

Uncommon
Immune system: hypersensitivity reactions, including rash, eczema with severe itching and lump formation (urticaria), inflammation of the skin (erythema) or itching (pruritus).
Gastrointestinal tract: metallic setting on the gums.
Skin: loss of hair (alopecia).
Reproductive system and breasts: dysfunctional spermatogenesis and ovulation, and painful gynaecomastia.

Rare
Blood: haemolytic anaemia, suppression of the bone marrow characterised by a severe decrease of white blood cells, combined with high fever, severe sore throat and mouth ulcers (agranulocytosis), as well as anaemia as a result of decreased blood cell production.
Immune system: severe hypersensitivity with low blood pressure (hypotension), accelerated heartbeat (tachycardia), breathing difficulties (dyspnoea), distress as a result of muscle cramps in the airways (bronchospasms), swelling of the face and fever; suppression of the immune system (immunosuppression).
Nutrition and metabolism: reduced level of electrolytes (calcium, magnesium, sodium, phosphate, potassium) in the blood with muscle cramping and/or changes in an electrocardiogram (ECG); excessive cholesterol levels in the blood. Increased blood amylase (enzyme) levels.
Nervous system: 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.
Eyes: loss of sight (blindness), difficulties in colour perception and eye movement dysfunction.
Hearing: unable to hold normal conversation, loss of hearing (in particular among children and elderly patients).
Heart: increased blood pressure levels and heart attacks.
Gastrointestinal tract: inflammation of mucous membranes of the mouth (stomatitis).
Liver and bile: reduced blood protein levels (albumin).
Cisplatin, like other similar medicines, increases the risk of leukaemia (secondary leukaemia).

Very rare
Hormones: insufficient production of the vasopressin hormone in the brain.
Nutrition and metabolism: increased iron levels in the blood.
Nervous system: attacks (seizures).
Eyes: swelling (papilloedema), inflammation of the eye nerve combined with pain and reduced nerve function (optic neuritis), blindness as a result of brain dysfunction.
Heart: heart arrest.
Blood vessels: blood flow dysfunction, e.g. in the brain, but also in the fingers and toes.
Skin and dermis: baldness due to hair loss.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CISPLATIN

Keep Cisplatin out of the reach and sight of children.
Do not store above 25°C.
Do not refrigerate or freeze.
Keep the vial in the outer carton (to avoid exposure of Cisplatin to light).

Use by date: Do not use Cisplatin after the expiry, which is stated on the carton and vial after "EXP".

Do not use Cisplatin if you notice visible signs of deterioration.

6. FURTHER INFORMATION

Each millilitre (ml) of solution contains 1 milligram (mg) of cisplatin.
The 10 ml vial contains 10 mg cisplatin, the 20 ml vial contains 20 mg cisplatin, the 50 ml vial contains 50 mg cisplatin and the 100 ml vial contains 100 mg.

What Cisplatin contains

- The active substance is cisplatin.
- Other ingredients are sodium chloride, dilute hydrochloric acid and water for injections

What Cisplatin looks like and contents of the pack
Cisplatin is a clear and colourless to yellowish solution for infusion in glass injection vials.
Packaging with 1, 5 or 10 injection vial(s) of 10 ml, each injection vial containing 10 mg cisplatin.
Packaging with 1, 5 or 10 injection vial(s) of 20 ml, each injection vial containing 20 mg cisplatin.
Packaging with 1, 5 or 10 injection vial(s) of 50 ml, each injection vial containing 50 mg cisplatin.
Packaging with 1, 5 or 10 injection vial(s) of 100 ml, each injection vial containing 100 mg cisplatin.

Some of the packaging sizes will not be for sale.

Marketing authorisation holder and manufacturer:

PA 789/2/5

Marketing authorisation holder:
Ebewe Pharma Ges.m.b.H Nfg. KG
Mondseestrasse 11
A-4866 Unterach
Austria

Manufacturer:

EBEWE Pharma Ges.m.b.H. Nfg.KG
Mondseestrasse 11

4866 Unterach
Austria

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

Netherlands
Cisplatine Sandoz 1 mg/ml, concentraat voor oplossing voor infusie

Belgium
Cisplatine Sandoz 1mg/ml, concentraat voor oplossing voor infusie

Denmark
Cisplatin "Meda", koncentrat til infusionsvæske, opløsning 1mg/ml

Finland
Cisplatin "Ebewe" 1mg/ml infuusiokonsentratti, liuosta varten

Germany
Cisplatin Neocorp 1 mg/ml - Konzentrat zur Herstellung einer Infusionslösung

Greece
Cisplatin “Ebewe” 1mg/ml Cs.Inj.Sol.

Ireland
Cisplatin "Ebewe" 1mg/ml - Concentrate for Solution for Infusion

Italy
Cisplatino Sandoz 1mg/ml – concentrato per soluzione per infusione

Luxembourg
Cisplatine Christiaens 1mg/ml

Portugal
Cisplatina Generis 1mg/ml

Spain
CISPLATINO Sandoz 1mg/ml concentrado para solución para perfusión

Sweden
Cisplatin Ebewe 1mg/ml, koncentrat till infusionsvätska, lösning

United Kingdom
Cisplatin 1mg/ml, Injection BP

This leaflet was last approved in May 2013

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

Special precautions for disposal and other handling
Cisplatin is to be diluted before use. For preparation of solution for infusion, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided.
Preparation of solution for infusion must take place in aseptic conditions.
For dilution of the concentrate, one of the following solutions should be used:
- sodium chloride solution 0.9%;
- mixture of sodium chloride solution 0.9% and glucose solution 5% (1:1)
  (resulting final concentrations: sodium chloride 0.45%, glucose 2.5%).
- Should hydration prior to the treatment with cisplatin be impossible, the concentrate may be diluted with:
  mixture of sodium chloride solution 0.9% and mannitol solution 5% (1:1)
  (resulting final concentrations: sodium chloride 0.45%, mannitol 2.5%).

Preparation of cisplatin solution for infusion:
The required amount (dose) of the cisplatin should be diluted in 1-2 litres of one of the above mentioned solutions.

The diluted solution should be administered only by intravenous infusion.
Only clear and colourless to yellowish solutions without visible particles should be used.

For single use only.

Cytotoxic agents should be prepared for administration only by personnel who have been trained in the safe handling of the preparation.

Refer to local cytotoxic handling guidelines.

As any other cytotoxic agent, cisplatin should be used with extreme caution: gloves, face masks and protective clothing are required and vital. Cisplatin should be processed under a protective hood, if possible. Contact with skin and/or mucous membranes must be avoided. Pregnant hospital employees should not work with cisplatin.

Skin contact: Rinse with large quantities of water. Apply an ointment if you have a temporary burning feeling. (Note: Some persons are sensitive to platinum and may experience a skin reaction).

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. In the case of spillage all items coming into contact with Cisplatin should be handled and disposed in accordance to local cytotoxic guidelines.

Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

Cisplatin reacts with aluminium which results in production of a black platinum precipitate. Therefore any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided.

This medicinal product must not be mixed with other medicinal products except those mentioned above.

The cisplatin must not be diluted with glucose solution 5% alone or mannitol solution 5% alone, but only with the mixtures containing additionally sodium chloride as stated above.

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

Special precautions for storage

Medicinal product as packaged for sale:

Do not store above 25 C. Do not refrigerate or freeze. Keep the vial in the outer carton.

Solution for infusion after dilution:

Chemical and physical in-use stability has been demonstrated for 48 hours at 2 to 8°C for solutions with a final cisplatin concentration of 0.1 mg/ml after dilution of the cisplatin concentrate with one of the following solutions:

- sodium chloride solution 0.9%;
- mixture of sodium chloride solution 0.9% and glucose solution 5% (1:1);
- mixture of sodium chloride solution 0.9% and mannitol solution 5% (1:1).

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, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.