Package leaflet: Information for the patient

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, 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

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 can destroy cells in your body that may cause certain types of cancer (tumor of testis, tumor of ovary, tumor of the bladder, head and neck epithelial tumor, lung cancer and for 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);
- you are allergic 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 nerve damage caused by cisplatin;
- you are breast-feeding;
- combined with certain types of vaccines such as yellow fever vaccine or phenytoin (a medicine used to prevent seizures) (see "Other medicines and Cisplatin below).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Cisplatin.
- if you have an increased amount of uric acid or proteins in your blood, which may be seen in blood tests (these may predispose to cisplatin-induced nephrotoxicity).
- if you suffer from a nerve damage (tingling or numbness of hands and feet) not caused by cisplatin.
- if you have received radiotherapy to the head.
- if you suffer from an infection.
- if you intend to have children (see Pregnancy, breast-feeding and fertility). You should use effective methods of contraception during and for at least 6 months after treatment with cisplatin.

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

Monitoring before and during treatment:
Your doctor should 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. The tests may be carried out on a weekly basis over the entire duration of your treatment.
Your hearing will be tested prior to each treatment with Cisplatin.

During treatment:
If spillage of cisplatin occurs, 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. Cisplatin on the skin can result in tissue damage (cellulitis, fibrosis and necrosis).

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

Please note that these statements may also apply to medicines used some time ago or at some time in the future.
- Use of medicines that inhibit the **bone marrow** function or radiation can increase the adverse effects of cisplatin on the bone marrow.
- The toxicity of bleomycin and methotrexate (other medicines for **cancer treatment**) may increase when administered with/or after cisplatin because of potentially reduced renal elimination caused by cisplatin nephrotoxicity.
- 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 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 **antifungals**: amphotericin B) and **contrast agents** (used in medical imaging).

- Cisplatin toxicity may also affect hearing when administered with **aminoglycosides**.
- If you use medicines to treat **gout** during your treatment with cisplatin, then the dose of such medicines may need to be adjusted (e.g. allopurinol, cholchicine, probenecid and/or sulfinpyrazone) as cisplatin may cause an increase in uric acid content in your blood.
- Administration of drugs that elevate your rate of bodily urine excretion (**loop diuretics**) combined with cisplatin (where the cisplatin dose is not more than 60mg/m² and urine secretion is not 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, feeling or being sick, mental problems (**antihistamines**, such as buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes and/or trimethobenzamides).
- Cisplatin given in combination with **ifosfamide** may result in hearing impairment, increased loss of proteins from your body and increased toxicity to kidneys.
- Administration of **pyridoxine** and **altretamine** may reduce the effect of cisplatin therapy.
- 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 amount of certain medicines used to treat epilepsy (such as **phenytoin**) in your blood thereby reducing the effect on the treatment of epilepsy. You should not start a new treatment for epilepsy while you are on cisplatin therapy (see "Do not use Cisplatin")
- **Penicillamine** may reduce the effectiveness of Cisplatin
- Cisplatin may have an adverse impact on the effectivness of agents preventing coagulation (**anticoagulants**). Therefore, coagulation should be checked more often during combined use.
- Cisplatin in combination with **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 (including yellow fever vaccinations) when undergoing treatment or within three months after the end of treatment with cisplatin (see "Do not use 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, pharmacist or nurse for advice before taking this medicine.

Cisplatin must not be used during **pregnancy** unless clearly indicated by your doctor.
You must use effective contraception if you are of child-bearing age during and at least 6 months after treatment with cisplatin.

You must not breast-feed while you are being 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 counseling 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 9 mg sodium per ml.
To be taken into consideration by patients on a controlled 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 that may also contain glucose.

Cisplatin is only given by injection into a vein (an intravenous infusion). The prepared infusion should be administered over a period of 6 to 8 hours. There must be support equipment for bringing under control allergic reactions.

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

Cisplatin is recommended for children, adolescents and adults.
The recommended dose 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 recommended doses are:
- A *single* dosage of 50 to 120 mg/m² body surface, every 3 to 4 weeks.
- 15 to 20 mg/m² per day for 5 days, every 3 to 4 weeks.

Cisplatin in combination with other chemotherapeutical agents (combination chemotherapy):
The recommended dose is 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/m^2 weekly for 6 weeks.

Your doctor may reduce the dose if you have kidney problems or problems with your bone marrow.

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 which may include kidney failure, liver failure, deafness, changes to vision, reduced production of blood cells and conditions such as feeling sick, being sick and inflammation of nerves. 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, pharmacist 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.

If any of the following side effects happen, you may need urgent medical attention.

Tell your doctor immediately, if you notice any of the following:

- sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, mouth or throat, shortness of breath or wheezing, increased heart rate and fall in blood pressure,
- reduction in number of all types of blood cells due to depression of bone marrow including white blood cells (which may cause an increase in infections or fever e.g. sore throat, mouth ulcers that you get), red blood cells (which can make the skin pale and cause weakness or breathlessness) and platelets (which increases the risk of bruising and bleeding (thrombocytopenia)),
- a disease condition characterised by reduction in the number of red blood cells, platelets and kidney failure (haemolytic uraemic syndrome),
- suppression of the immune system which may cause more frequent infections, blood poisoning (sepsis) may occur,
- over production of a hormone causing fluid and sodium retention, resulting in weakness, tiredness or confusion,
- damage to the nervous system, characterised by tickling, itching or tingling without cause,
- fits, loss of certain types of brain function, including brain dysfunction characterised by spasms and reduced levels of consciousness,
- damage to part of the brain due to bleeding or reduced blood supply which may cause weakness of the arms or legs, headache, dizziness and confusion, difficulty swallowing and slurred speech (stroke),
- a rapid increase in abnormal white blood cells (symptoms may include feeling very tired, bleeding bruising and increased risk of infections),(acute leukaemia),
- problem with the spinal cord, which can lead to numbness, weakness, loss of balance, pain in the back, neck and legs,
- loss of certain functions of brain which can lead to excessive fatigue, rapid or slow heart rate, blood pressure fluctuations, shortness of breath and abdominal distention,

- inflammation of the eye nerve combined with pain and reduced nerve function,
- loss of sight (blindness), swelling of nerves at the back of the eye,
- loss of hearing or deafness,
- a block in the blood vessels of the heart causing chest pain which may spread to the neck shoulders or jaw (heart attack),
- disease of the blood vessels of heart which may be due to thickening of the walls of these blood vessels thereby narrowing it and restricting blood flow to heart,
- infection of the lungs which may cause fever, chills, shortness of breath, cough, phlegm and coughing up blood (pneumonia) or respiratory failure,
- blockage of blood vessels in the lungs,
- kidneys problems (you may notice pain in the back, little or no urine being produced or the urine may be cloudy or have blood in it) or kidney failure,
- infection or injury at the site of infusion.

Other possible side effects may occur:

Very common (may affect more than 1 in 10 people)
Reduced level of sodium in your blood, which may be seen in blood tests, fever.

Common (may affect up to 1 in 10 people)
Change in your heartbeats (arrhythmia), including reduced heartbeat (bradycardia), accelerated heartbeat (tachycardia), inflammation of a vein (phlebitis), shortness of breath (dyspnoea), redness and ulceration of the skin, swelling (oedema) and pain at the site of injection, scaring may also occur.

Uncommon (may affect up to 1 in 100 people)
Low level of magnesium in your blood, which may be seen in blood tests, decreased sperm count and abnormal ovulation, painful breast growth in men (gynaecomastia)

Rare (may affect up to 1 in 1,000 people)
Excessive cholesterol levels in the blood, eye movement dysfunction, increased blood pressure levels (hypertension), inflammation of mucous membranes of the mouth, decreased in blood proteins.

Very rare (may affect up to 1 in 10,000 people)
Increased iron levels in the blood.

Not known (frequency cannot be estimated from the available data)
*I*ncreased blood amylase (enzyme) and liver enzymes levels, increased amount of bilirubin (a substance released due to break down of red blood cells) in our blood, which may be seen in blood tests, reduced level of electrolytes (calcium, phosphate, potassium) in the blood with muscle cramping and/or changes in an electrocardiogram (ECG), increased amount of uric acid in your blood, dehydration, involuntary contraction of muscles (tetany), loss of taste, sudden shooting pains from the neck through the back into the legs when bending forwards, difficulties in colour perception, blurred vision, pigmentation of inner part of your eyes which may lead to blindness, ringing in the ears (tinnitus), heart disorder, changes in blood flow to the fingers and toes causing blue coloration of skin (Raynaud´s syndrome), loss of appetite, feeling sick, being sick, diarrhoea, hiccups, loss of hair, rash, muscle cramps/spasms, weakness (asthenia), generally feeling unwell (malaise).

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
IRELAND
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 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.

After dilution:
In-use stability has been demonstrated for 14 days at 15-25°C under protection from light.

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 has taken place in controlled and validated aseptic conditions.

Do not use this medicine if you notice that the solution is cloudy or has a deposit that does not dissolve. In this case, the vial should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of 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 50 ml concentrate for solution for infusion contains 50 mg cisplatin.

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

The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) 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 free from visible particles in glass injection vials.

Packaging with 1 vial of 50 ml of concentrate, the vial containing 50 mg cisplatin.
Packaging with 1 vial of 100 ml of concentrate, the vial containing 100 mg cisplatin.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Generics [UK] Limited
Station close, Potters Bar,
Hertfordshire EN6 1TL
United Kingdom

Manufacturer
Strides Arcolab Polska Sp.z.o.o.
10, Daniszewska Str
03-230 Warsaw
Poland

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

Member State	**Name of the medicinal product**
The Netherlands (RMS)	Cisplatine Mylan 1 mg/ml concentraat voor oplossing voor infusie
Austria	Cisplatin Mylan 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Cisplatine Mylan 1 mg/ml concentraat voor oplossing voor infusie
Bulgaria	Cisplatin Mylan 1 mg/ml концентрат за инфузионен разтвор
Cyprus	Cisplatin Mylan 1 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Czech Republic	Cisplatina Mylan 1 mg/ml koncentrát pro infuzní roztok
Germany	Cisplatin Mylan 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Denmark	Cisplatin Mylan 1 mg/ml koncentrat til infusionsvaeske, opløsning.
Estonia	CisplatinMylan 1 mg/ml, infusioonilahuse kontsentraat
Greece	Cisplatin/Mylan 1 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Finland	Cisplatin Mylan 1 mg/ml infuusiokonsentraatti, liuosta varten

France	Cisplatin Mylan Pharma 1 mg/ml solution à diluer pour perfusion
Hungary	Cisplatin Mylan 1 mg/ml koncentrátum oldatos infúzióhoz.
Ireland	Cisplatin 1 mg/ml concentrate for solution for infusion
Iceland	Cisplatin Mylan1 mg/ml, innrennslisþykkni, lausn
Italy	Cisplatino Mylan
Latvia	Cisplatin Mylan 1mg/ml koncentrāts infūziju šķīduma pagatavošanai
Lithuania	Cisplatin Mylan 1 mg/ml koncentratas infuziniam tirpalui.
Luxemburg	Cisplatine Mylan 1 mg/ml solution à diluer pour perfusion
Malta	Cisplatin Mylan 1mg/ml konċentrat għal soluzzjoni għall-infużjoni
Norway	Cisplatin Mylan 1 mg/ml, konsentrat til infusjonsvæske.
Poland	Cisplatin Mylan, 1 mg/ml, koncentrat do sporządzania roztworu do infuzji
Portugal	Cisplatina Mylan 1 mg/ml concentrado para solução para perfusão
Romania	Cisplatin Mylan 1 mg/ml concentrat pentru soluție perfuzabilă
Spain	Cisplatino Mylan 1 mg/ml concentrado para solución para perfusión
Sweden	Cisplatin Mylan 1 mg/ml koncentrat till infusionsvätska, lösning
Slovak Republic	Cisplatina Mylan 1 mg/ml infúzny koncentrát
Slovenia	Cisplatin Mylan 1 mg/ml koncentrat za raztopino za infundiranje
UK	Cisplatin 1 mg/ml, concentrate for solution for infusion

This leaflet was last approved in *{09/2015}*

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 9mg/ml (0.9%)/ glucose 50mg/ml (5%) (1:1), (resulting final concentrations: sodium chloride 4.5mg/ml (0.45%), glucose 25mg/ml (2.5%));
- sodium chloride 9mg/ml (0.9%) and 18.75mg/ml (1.875%) mannitol, for injection;
- sodium chloride 4.5mg/ml (0.45%), glucose 25mg/ml (2.5%) and 18.75mg/ml (1.875%) mannitol, for injection.

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), sulfates, 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 14 days at 15-25°C under protection from light.
From a microbiological point of view, the product should always be used immediately.