PACKAGE LEAFLET: INFORMATION FOR THE USER

CISPLATIN TEVA 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 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 Teva 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 (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. Before you are given Cisplatin Teva

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 platinum 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 breastfeeding
- combined with yellow fever vaccine and phenytoin (see “Other medicines and Cisplatin” below).

Warnings and precautions

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 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 suffer from vomiting and diarrhoea after administration of Cisplatin the liquid loss must be compensated.
- 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/using, have recently taken/used or might take/use 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.
- 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 ifosfamide may result in hearing impairment or toxic effects on kidneys.
- 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 (also see "Do not use Cisplatin").
- 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 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 must not receive yellow fever vaccinations (also 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 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 breastfeed 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 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 Teva contains sodium
Cisplatin Teva contains 3.5 mg sodium per ml. This should be considered by patients on a controlled sodium diet.

3. How you are given Cisplatin Teva

Dosage and method of administration
Cisplatin should only be given by a specialist in cancer treatment. The concentrate will be diluted before it is given to you.

Cisplatin is only given by 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).

<u>Cisplatin Teva (monotherapy):</u>
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 Teva 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/m^2 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 Teva 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, contact your doctor immediately.

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.

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.

Other possible side effects

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), as well as reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness (anaemia). The bone marrow does not make enough blood cells, or none at all (bone marrow failure)
- reduced level of the electrolyte sodium
- loss of hearing combined with tinnitus
- loss of appetite (anorexia), nausea, vomiting, diarrhoea
- 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)
- fever.

Common: may affect up to 1 in 10 people
- infections and blood-poisoning (sepsis)

- 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)
- 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
- deafness and dizziness
- arrhythmia, including reduced heartbeat (bradycardia), accelerated heartbeat (tachycardia)
- inflammation of a vein (phlebitis)
- shortness of breath (dyspnoea), inflammation of the lungs (pneumonia) and respiratory failure
- liver dysfunction
- redness and inflammation of the skin (erythema, skin ulcer) in the area of the injection
- swelling (oedema) and pain at the area of injection.

Uncommon: may affect up to 1 in 100 people
- hypersensitivity reactions, including rash, eczema with severe itching and lump formation (urticaria), redness and inflammation of the skin (erythema) or itching (pruritus)
- reduced level of the electrolyte magnesium
- metallic setting on the gums
- loss of hair (alopecia)
- dysfunctional spermatogenesis and ovulation, and painful breast growth in men (gynaecomastia)
- hiccups, weakness (asthenia), malaise.

Rare: may affect up to 1 in 1,000 people
- cancer of blood-forming cells in the bone marrow, characterised by the rapid growth of abnormal white blood cells (acute leukaemia). Cisplatin, like other similar medicines, increases the risk of leukaemia (secondary leukaemia)
- 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
- severe hypersensitivity (anaphylactic reactions) 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)
- increased blood amylase (enzyme) levels
- reduced level of electrolytes (calcium, phosphate, potassium) in the blood with muscle cramping and/or changes in an electrocardiogram (ECG). Excessive cholesterol levels in the blood
- loss of certain types of brain function, including brain dysfunction characterised by spasms and reduced levels of consciousness (encephalopathy), degeneration of the white matter in the brain (leukoencephalopathy), as well as closure of the carotid artery; convulsion; symptoms such as headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss (reversible posterior leukoencephalopathy syndrome)
- loss of sight (blindness), difficulties in colour perception and eye movement dysfunction
- unable to hold normal conversation, loss of hearing (in particular among children and elderly patients)
- increased blood pressure levels, coronary artery disease and heart attacks
- inflammation of mucous membranes of the mouth (stomatitis)
- reduced blood protein levels (albumin).

Very rare: may affect up to 1 in 10,000 people
- insufficient production of the vasopressin hormone in the brain (SIADH)
- increased iron levels in the blood
- attacks (seizures)

- swelling of the optic disc (papilloedema), inflammation of the eye nerve combined with pain and reduced nerve function (optic neuritis), blindness as a result of brain dysfunction
- heart arrest
- blood flow dysfunction, e.g. in the brain, but also in the fingers and toes (Raynaud´s syndrome).

Not known: frequency cannot be estimated from the available data
- dehydration, increased uric acid level (hyperuricaemia), syndrome characterised by muscle cramps (tetany)
- cerebrovascular accident, stroke (haemorrhagic or ischaemic), loss of taste (ageusia)
- blurred vision, colour blindness, retinal disorder
- heart problems
- changes to the kidneys and blood (haemolytic uraemic syndrome)
- blood clot in the lungs which causes chestpain and breathlessness (pulmonary embolism)
- rash
- muscle spasms
- acute dysfunction of the kidneys.

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 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 Teva

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

Keep the vial in the outer carton in order to protect from light.

Store at 15°C-25°C. If the product is stored below 15°C a precipitation may occur. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used.

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.

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 Teva contains
The active substance is cisplatin.
Cisplatin Teva 1 mg/ml, concentrate for solution for infusion contains 1 mg cisplatin per ml.
Other ingredients are sodium chloride, dilute hydrochloric acid (for pH adjustment), dilute sodium hydroxide (for pH adjustment) and water for injections

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

Cisplatin Teva 1 mg/ml:
Packaging with 1 injection vial of 10 ml, each injection vial containing 10 mg cisplatin.

Packaging with 1 injection vial of 50 ml, each injection vial containing 50 mg cisplatin.
Packaging with 1 injection vial of 100 ml, each injection vial containing 100 mg cisplatin.

Not all pack sizes may be marketed.

Manufacturer
Pharmachemie B.V.
Swensweg 5, Postbus 552, 2003 RN Haarlem
The Netherlands

Teva Pharmaceutical Works Private Limited Company
Táncsics M. út 82, H-2100 Gödöllő,
Hungary

Marketing authorisation holder
Teva Pharma B.V.
Swensweg 5
2031GA Haarlem
The Netherlands.

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

The Netherlands	Cisplatine 1 mg/ml PCH, concentraat voor oplossing voor infusie
Belgium	Cisplatine Teva 1 mg/ml concentraat voor oplossing voor infusie
Denmark	Cisplatin TEVA
Germany	Cisplatin Teva 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Greece	Platosin
Ireland	Cisplatin Teva 1 mg/ml, concentrate for solution for infusion
Italy	Cisplatino Teva Italia 1 mg/ml concentrato per soluzione per infusione
Luxembourg	Cisplatine Teva 1 mg/ml solution à diluer pour perfusion
Malta	Cisplatin Teva 1 mg/ml
Poland	Cisplatin Teva
Portugal	Cisplatina Teva 1 mg/ml concentrado para solução para perfusão - IV
Romania	Platosin 1 mg/ml, concentrat pentru soluţie perfuzabilă
United Kingdom	Cisplatin 1 mg/ml concentrate for solution for infusion

This leaflet was last revised in April 2017.

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

Preparation and handling of the product
Like with all anti-neoplastic products caution is needed with the processing of cisplatin. Dilution should take place under aseptic conditions by trained personnel in an area specifically intended for this. Protective gloves should be worn for this. 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.

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.

Incompatibilities
Do not bring in contact with aluminium. Cisplatin may interact 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.

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 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
- sodium chloride 0.45%, glucose 2.5% and 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.

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.

Special precautions for storage
Undiluted solution (Medicinal product as packaged for sale):
*S*tore at 15°C-25°C. Keep the vials in the outer carton in order to protect from light. If the undiluted solution is stored below 15°C a precipitation may occur. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used.

After dilution:
Do not refrigerate or freeze the diluted solution.

After dilution in infusion fluids, the product can be stored for at most 14 days at room temperature (15°C–25 °C) under protection from light.

Exposure to ambient light must be limited to at most 6 hours. If exceeding 6 hours, the bags must be thoroughly wrapped in aluminium foil in order to protect the contents from ambient 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.