The name of your medicine is ‘Cisplatin 1 mg/ml Concentrate for Solution for Infusion’ but in the rest of the leaflet it will be called “Cisplatin Injection.”

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

1. What Cisplatin Injection 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, tumour of the bladder, head and neck epithelial tumour, 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 Injection

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 ifosfamide 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 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 or pharmacist for advice before taking 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.

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 injection contains sodium
Cisplatin contains 3.5 mg sodium per ml. This should be considered if you have to keep to a low sodium diet.

3. How to use Cisplatin Injection

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 contains glucose.
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 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 take 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, 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.

The following side effects may occur:

**Very common (may affect more than 1 in 10 people)**

**Blood and lymphatic system:** suppression of the bone marrow characterised by a severe decrease 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).

**Nutrition and metabolism:** reduced level of electrolytes (sodium)

**Gastrointestinal tract:** loss of appetite (anorexia), nausea, vomiting, diarrhoea.

**Kidneys and urinary tracts:** excessive uric acid levels (hyperuricaemia) in the blood (e.g. gout).

**General symptoms:** fever.

**Common (may affect up to 1 in 10 people)**

**Infections:** blood-poisoning (sepsis).

**Heart:** arrhythmia, including reduced heartbeat (bradycardia), accelerated heartbeat (tachycardia).

**Blood vessels:** inflammation of a vein (phlebitis) at injection site.

**Respiratory disorders:** difficulty of breathing (dyspnoea), inflammation of the lungs (pneumonia) and respiratory failure.

**Uncommon (may affect up to 1 in 100 people)**

**Immune system:** hypersensitivity 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)

**Hearing:** damage to the ear (ototoxicity)

**Nutrition and metabolism:** reduced level of electrolytes (Magnesium)

**Gastrointestinal tract:** metallic setting on the gums.

**Skin:** loss of hair (alopecia).

**Reproductive system and breasts:** dysfunctional spermatogenesis and ovulation, and painful breast growth in men (gynaecomastia).

**Rare (may affect up to 1 in 1,000 people)**

**Immune system:** 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).

**Nervous system:** loss of certain types of brain function, including brain dysfunction characterised by spasms and reduced levels of consciousness (encephalopathy), 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, sudden shooting pains from the neck through the back into the legs when bending forwards, attacks (seizures).

**Hearing:** unable to hold normal conversation, loss of hearing (in particular among children and elderly patients).

**Heart:** increased blood pressure levels, coronary artery disease and heart attacks.

**Liver and bile:** reduced albumin (protein) levels in blood

**Gastrointestinal tract:** inflammation of mucous membranes of the mouth (stomatitis)

**General:** Cisplatin, like other similar medicines, increases the risk of leukaemia (acute leukaemia).

**Very rare (may affect up to 1 in 10,000 people)**

**Nutrition and metabolism:** increased iron levels in the blood.

**Heart:** heart(cardiac) arrest.
Infections: Infection
Blood and lymphatic system: haemolytic anaemia
Hormones: insufficient production of the vasopressin hormone in the brain (SIADH), blood amylase (enzyme) increased.
Nutrition and metabolism: 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.
Nervous system: spinal disease, brain dysfunction (confusion, slurred speech, sometimes blindness, memory loss, and paralysis); stroke, loss of taste (ageusia), as well as closure of the carotid artery.
General symptoms: weakness (asthenia), malaise, dehydration, swelling (oedema), pain, redness and inflammation of the skin (erythema, skin ulcer) at the area of injection
Kidneys and urinary tracts: kidney dysfunction, such as failure to produce urine (anuria) and urine poisoning of the blood (uraemia)
Musculo skeletal: muscle spasms
Skin and dermis: hair loss, rash
Liver and bile: liver dysfunction, liver enzymes increased, bilirubin increased.
Gastrointestinal tract: blood flow dysfunction, e.g. in the brain, but also in the fingers and toes (Raynaud’s syndrome), Thrombotic microangiopathy combined with haemolytic uraemic syndrome.
Heart: cardiac disorder
Hearing and balance function: loss of hearing combined with tinnitus (ringing in ears)
Eyes: blurred vision, difficulties in colour perception and eye movement dysfunction, swelling (papilloedema), inflammation of the eye nerve combined with pain and reduced nerve function (optic neuritis), blindness as a result of brain dysfunction.

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 at: www.mhra.gov.uk/yellowcard.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cisplatin injection

Keep this medicine out of sight and reach of children.
Keep the vial in the outer carton (to avoid exposure of Cisplatin to light).

Concentrate for solution for infusion 1 mg/ml
Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze.
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.
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
If you find the solution cloudy or a deposit that does not dissolve is noticed, the bottle should be discarded.

6. Contents of the pack and other information

What Cisplatin Injection contains:
Cisplatin Injection contains the active ingredient cisplatin.
Each millilitre (ml) of solution contains 1 milligram (mg) of cisplatin. This medicine is presented in amber glass containers called vials.

<table>
<thead>
<tr>
<th>Presentations</th>
<th>10 ml</th>
<th>25 ml</th>
<th>50 ml</th>
<th>100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of cisplatin</td>
<td>10 mg</td>
<td>25 mg</td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

It is available in packs containing a single vial (not all the presentations mentioned may be marketed).
The other ingredients include water for injections, sodium chloride, hydrochloric acid (for pH adjustment) and/or sodium hydroxide (for pH adjustment).

**What Cisplatin Injection looks like and content of the pack:**
Cisplatin Injection is clear, colourless to pale yellow solution in an amber glass vial practically free from particles with flip off transparent seal.

Packaging with 1 injection vial of 10 ml, each injection vial containing 10 mg cisplatin.
Packaging with 1 injection vial of 25 ml, each injection vial containing 25 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.

**Marketing Authorisation Holder and manufacturer:**
Accord Healthcare Limited,
Sage House, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF,
United Kingdom.

This leaflet was last revised in 02/2016.
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. Cisplatin should not be used during pregnancy unless the clinician considers the risk in an individual patient to be clinically justified.

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 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.

With respect to microbiological, chemical and physical stability with use of the undiluted solutions, see below “Special precautions for storage”.

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. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

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.

Special precautions for storage
Medicinal product as packaged for sale:
**Concentrate for solution for infusion 1 mg/ml**

Undiluted solution: Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used.

**Diluted solution:**
For the storage condition of the diluted medicinal product: see below
“Concentrate for solution for infusion after dilution”.
Do not refrigerate or freeze.

**Concentrate for solution for infusion after dilution:**

*After dilution*

Chemical and physical in-use stability after dilution with infusion fluids described in section “Preparation and handling of the product”, indicate that after dilution with recommended intravenous fluids, Cisplatin Injection remains stable for 24 hours at 20 - 25 °C room temperature.

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.