1. NAME OF THE MEDICINAL PRODUCT

Cisplatin "Ebewe"

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 0.5mg cisplatin as active ingredient.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
The concentrate is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To be used as mono-therapy, or as part of an existing chemotherapy for advanced or metastatic tumours: testicular carcinoma (palliative and curative poly-chemotherapy) and ovary carcinoma (stages III and IV), and head and neck squamous-cell epithelioma (palliative therapy).
Additionally efficacy was reported in: lung carcinoma, urothelialtract cancer, cervical tumor.

4.2 Posology and method of administration

Cisplatin "Ebewe" 0.5mg/ml concentrate for solution for infusion is to be diluted before use (see section 6.6.). The diluted solution should be administered only intravenously by infusion (see below). For administration, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided (see section 6.2.).

Adults and children:

The cisplatin dosage depends on the primary disease, the expected reaction, and on whether cisplatin is used for monotherapy or as a component of a combination chemotherapy. The dosage directions are applicable for both adults and children.
For mono-therapy, the following two dosage regimens are recommended:
- Single dose of 50 to 120mg/m^2 body surface every 3 to 4 weeks;
- 15 to 20mg/m^2/day for five days, every 3 to 4 weeks.

If cisplatin is used in combination chemotherapy, the dose of cisplatin must be reduced. A typical dose is 20 mg/m^2 or more once every 3 to 4 weeks.
For warnings and precautions to be considered prior to the start of the next treatment cycle, see section 4.4.
In patients with renal dysfunction or bone marrow depression, the dose should be reduced adequately.
The cisplatin solution for infusion prepared according to instructions (see section 6.6.) should be administered by intravenous infusion over a period of 6 to 8 hours.
Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydratation is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realised by intravenous infusion of one of the following solutions:
- sodium chloride solution 0.9%;
- mixture of sodium chloride solution 0,9% and glucose solution 5% (1:1).

Hydration prior to treatment with cisplatin:
intravenous infusion of 100 to 200ml/hour for a period of 6 to 12 hours.
Hydration after termination of the administration of cisplatin:
intravenous infusion of another 2 litres at a rate of 100 to 200 ml per hour for a period of 6 to 12 hours.
Forced diuresis may be required should the urine secretion be less than 100 to 200ml/hour after hydration.
Forced diuresis may be realised by intravenously administering 37.5g mannitol as a 10% solution (375ml mannitol solution 10%), or by administration of a diuretic if the kidney functions are normal. The administration of mannitol or a diuretic is also required when the administrated cisplatin dose is higher than 60mg/m^2 of body surface.
It is necessary that the patient drinks large quantities of liquids for 24 hours after the cisplatin infusion to ensure adequate urine secretion.

4.3 Contraindications

Cisplatin is contraindicated in patients
- with hypersensitivity to the active substance or other platinum containing medicinal products;
- with renal dysfunction;
- in dehydrated condition (pre- and post-hydration is required to prevent serious renal dysfunction);
- with myelosuppression;
- with a hearing impairment;
- with neuropathy caused by cisplatin and
- who are pregnant or breastfeeding (see section 4.6. Pregnancy and lactation).

4.4 Special warnings and special precautions for use

Cisplatin may only be administered under the supervision of a physician qualified in oncology with experience in the use of antineoplastic chemotherapy.
Cisplatin is proven to be cumulative ototoxic, nephrotoxic, and neurotoxic. The toxicity caused by cisplatin may be amplified by the combined use with other medicinal products, which are toxic for the said organs or systems.
Audiograms must be made before starting treatment with cisplatin and always before starting another treatment cycle.
Nephrotoxicity can be prevented by maintaining adequate hydration before, during and after the intravenous infusion of cisplatin.
Before, during and after administration of cisplatin, the following parameters resp. organ functions must be determined:
renal function;
hepatic function;
hematopoiesis functions (number of red and white blood cells and blood platelets);
serum electrolytes (calcium, sodium, potassium, magnesium).
These examinations must be repeated every week over the entire duration of the treatment with cisplatin.
Repeating administration of cisplatin must be delayed until normal values are achieved for the following parameters:
serum creatinine ≤ 130µmol/l rsp. 1.5mg/dl
urea < 25mg/dl
white blood cells > 4.000/µl resp. > 4.0 x 10^9/l
blood platelets > 100.000/µl resp. > 100 x 10^9/l
audiogram: results within the normal range.
Special caution must be exercised for patients with peripheral neuropathy not caused by cisplatin.
Special care is required for patients with acute bacterial or viral infections.
In cases of extravasation:
- immediately end the infusion of cisplatin;
- do not move the needle, aspirate the extravasate from the tissue, and rinse with sodium chloride solution 0.9% (if solutions with cisplatin concentrations higher than recommended were used; see section 6.6.).

Nausea, vomiting and diarrhoea often occur after administration of cisplatin (see section 4.8.).
Prophylactic administration of an anti-emetic may be effective in alleviating or preventing nausea and vomiting.
The liquid loss caused by vomiting and diarrhoea must be compensated.
Both male and female patients must use contraceptive methods to prevent conception and/or reproduction during and for at least 6 months after treatment with cisplatin. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. Since a treatment with cisplatin may cause irreversible infertility, it is recommended that men, who wish to become fathers in the future, ask for advice regarding cryo-conservation of their sperm prior to the treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous use of myelosuppressives or radiation will boost the effects of cisplatin's myelosuppressive activity.

The occurrence of nephrotoxicity caused by cisplatin may be intensified by concomitant treatment with antihypertensives containing furosemide, hydralazine, diazoxide, and propranolol.

It may be required to adjust the dosage of allopurinol, colchicine, probenecid, or sulfinpyrazone if used together with cisplatin, since cisplatin causes an increase in serum uric acid concentration.

Except for patients receiving doses of cisplatin exceeding 60mg/m^2, whose urine secretion is less than 1000ml per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.

Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes or trimethobenzamides may mask ototoxicity symptoms (such as dizziness and tinnitus).

Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides) or ototoxic (e.g. aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin on these organs. During or after treatment with cisplatin caution is advised with predominantly renally eliminated substances, e.g. cytostatic agents such as bleomycin and methotrexate, because of potentially reduced renal elimination.

Simultaneous use of ifosfamide causes increased protein excretion. The ototoxicity of cisplatin was reportedly enhanced by concomitant use of ifosfamide, an agent which is not ototoxic when given alone.

In a randomised trial in patients with advanced ovarian carcinoma the response to therapy was influenced negatively by concomitant administration of pyridoxine and hexamethylmelamine.

Evidence has been established that the treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 70–75%.

Reduction of the blood's lithium values was noticed in a few cases after treatment with cisplatin combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium values.

Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control.

Chelating agents like penicillamine may diminish the effectiveness of cisplatin.

No living virus vaccinations should be given within three months following the end of the cisplatin treatment.

4.6 Use during pregnancy and lactation

Cisplatin is suspected to cause serious birth defects when used during pregnancy. Cisplatin is contraindicated during the pregnancy period.

Women of child-bearing age should take contraceptives to prevent conception and/or reproduction during and for at least 6 months after treatment with cisplatin. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. For male patients please refer to Section 4.4. Special warnings and precautions for use.

Cisplatin was found in the milk of milk producing animals. Breastfeeding during the therapy is contraindicated.

4.7 Effects on ability to drive and use machines

Depending on individual susceptibility, the patient's ability to drive a vehicle or operate machinery may be impaired.

4.8 Undesirable effects

Undesirable effects depend on the used dose and may have cumulative effects.

Nephrotoxicity: a light and reversible renal dysfunction may be noticed after single use of an intermediary dose (20mg/m^2 to < 50mg/m^2). The use of a single high dose (50–120mg/m^2), or repeated daily use of cisplatin, may cause kidney insufficiency with tubular necrosis revealed as uremia or anuria. The kidney insufficiency may be irreversible.

The nephrotoxicity is cumulative and may occur 2–3 days, or two weeks after the first dose of cisplatin was used. The serum creatinine and urea concentrations may increase. However, the forced diuresis by hydration before and after the cisplatin administration decreases the nephrotoxicity risk. Nephrotoxicity was noticed in 28–36% of patients without sufficient hydration after a single dose of 50mg/m^2 of cisplatin.

Hyperuricaemia may occur asymptomatically or as gout. Hyperuricaemia has been reported in 25–30% of patients in conjunction with nephrotoxicity.

Myelosuppression: dose dependent, cumulative and mostly reversible leukopenia, trombocytopenia and anemia have been noticed. Cases were reported of Coombs' positive hemolytic anemia, which is reversible when the use of cisplatin is ended. Literature has been published regarding hemolysis possibly caused by cisplatin. Serious bone marrow depression (including agranulocytosis and/or aplastic anemia) may occur after using high doses of cisplatin. A considerable decrease in the number of white blood cells is often noticed approximately 14 days after the use (less than 1.5 × 10^9/l for 5% of the patients). A decrease of the number of blood platelets is noticed after approximately 21 days (less than 10% of the patients showed a total inferior to 50 × 10^9/l) (the recovery period is approximately 39 days).

Gastro-intestinal toxicity: anorexia, nausea, vomiting, stomach aches, and diarrhoea, often occur between 1 and 4 hours after the use. These symptoms disappear for most patients after 24 hours. Less serious nausea and anorexia may continue to occur up to seven days after the treatment. (See section 4.4.) Oral mucositis rarely occurs.

Ototoxicity: has been documented for approximately 30% of the patients treated with 50 mg/m² cisplatin. The defect is cumulative, may be irreversible, and is sometimes limited to one ear. Ototoxicity manifests itself as tinnitus and/or hearing impairment at higher frequencies (4,000–8,000 Hz). Hearing impairment at frequencies of 250–2000 Hz (normal hearing range) was noticed for 10 to 15% of the patients. Also deafness and vestibular toxicity combined with vertigo may occur. Earlier or simultaneous cranial radiation increases the risk of hearing loss. It rarely occurs that a patient loses the ability to conduct a normal conversation. Ototoxicity for children may be serious. (See section 4.4.)

Ocular toxicity: loss of eyesight rarely occurs in the course of a combination treatment with cisplatin. A papiledema with visual defects has been incidentally noticed, but is reversible after ending the treatment. Only one case of unilateral retrobulbar neuritis with loss of vision sharpness has been reported after poly-chemotherapy followed by a cisplatin treatment.

Neurotoxicity: neurotoxicity caused by cisplatin is characterised by peripheral neuropathy (typically bilateral and sensory), and rarely by the loss of taste or tactile function, or by retrobulbar neuritis with loss of sight and cerebral dysfunction (confusion, unclear speech, individual cases of cortical blindness, loss of memory, paralysis). Lhermitte's signs, autonomous neuropathy and myelopathy of the spinal cord have been noticed. Loss of the vital brain functions were reported (including one report of acute cerebrovascular complications, cerebral arteriitis, occlusion of the carotid artery, encephalopathy). The use of cisplatin should end immediately if one of the last mentioned cerebral symptoms occurs. Neurotoxicity caused by cisplatin may be reversible. However, the process is irreversible for 30–50% of the patients, even after ending the treatment. Neurotoxicity may occur after the first dose of cisplatin, or after a long-term therapy.

Serum electrolytes: hypomagnesemia, hypocalcemia, hyponatremia, hypophosphatemia and hypokalemia with muscle cramps and/or changes to the ECG rarely occur as a result of damage to the kidney tract caused by cisplatin, reducing the tubular resorption of these cations.

Allergic reactions: rare cases of anaphylactic reactions have been reported. They may occur as rashes, urticaria, erythema, or pruritus. Rare cases of hypotension, tachycardia, dyspnoea, bronchospasms, facial oedema and fever have been reported. Treatment with antihistamines, epinephrine (adrenaline) and steroids may be required.

Hepatic: liver dysfunction with increased serum transaminases rarely occurs and is reversible. Reduced albumin levels were rarely noticed and may be linked to the treatment with cisplatin.

Cardiac: cardiac rhythm disorders including bradycardia and tachycardia, and arrhythmia rarely occur. Changes of the ECG have rarely been observed. Cardiac arrest has been reported in extremely rare cases after a treatment with cisplatin combined with other cytostatic medicinal products.

Immune system: immunosuppression has been evidenced.

Other:

Local edema and pain, erythema, skin ulceration and phlebitis may occur in the area of the injection after intravenous administration.

A metallic setting on the gums has been noticed.

Alopecia, dysfunctional spermatogenesis and ovulation, and painful gynaecomastia may occur.

The development of secondary non-lymphatic leukaemia has been linked to the use of cisplatin.

Independent descriptions link vascular disorders (cerebral or coronary ischemia, impairment of the eripheral blood circulation related to the Raynaud's syndrome) to cisplatin including chemotherapy.

Carcinogenicity is theoretically possible, (based on cisplatin's mechanism of action), but not proven.

Hypercholesterolemia (rarely), inadequate ADH secretion (individual cases), increased amylase in the serum (rarely), trombotic microangiopathy combined with hemolytic-uremic syndrome (individual cases).

Increased iron concentrations have incidentally been registered.

4.9 Overdose

Overdoses are expected to cause the toxic activities as described hereinbefore to an excessive extent. Efficient hydration and osmotic diuresis may contribute to the reduction of the cisplatin toxicity, if used immediately after the overdose.

An overdose (≥ 200mg/m²) may directly affect the respiratory centre, which may cause fatal respiratory dysfunction and upsetting of the acid/base balance resulting from passing the blood-brain barrier.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents / platinum compounds ATC code: L01XA01

Cisplatin is an anorganic substance containing a heavy metal [cis-diamminedichlorophlatinum(II)]. This substance inhibits the DNA synthesis by realising transverse connections within and between the DNA strings. The protein and RNA synthesis is inhibited to a lesser extent.

Although the primary activity of cisplatin seems to be the inhibition of DNA synthesis, the antineoplastic process includes other activities, such as enlargement of the tumour immunogenicity. Cisplatin's oncolytic functions can be compared to the functions of alkylating substances. Cisplatin also offers immunosuppressive, radiosensitising and antibacterial features.

Cisplatin does not seem to be cell cycle specific.

The cytotoxic activities of cisplatin are caused by binding all DNA bases, with a preference for the N-7 position of guanine and adenosine.

5.2 Pharmacokinetic properties

After intravenous administration, cisplatin is rapidly distributed among all tissues. Following cisplatin doses of 20 to 120mg/m², the concentrations of platinum are highest in liver, prostate and kidney, somewhat lower in bladder, muscles, testicle, pancreas and spleen and lowest in bowel, adrenal, heart, lung, cerebrum and cerebellum. Over 90% of the total plasma cisplatin is bounded with protein after two hours following the administration. This process may be irreversible. The protein-bounded part is not antineoplastic active.

Cisplatin is non-linearly pharmacokinetic. Cisplatin is converted by a non-enzymatic process into one or more metabolites. Elimination from the plasma is realised in two phases after intravenous bolus injection of 50–100mg/m² of cisplatin. The following half-life period have been registered for humans:

t ½ (distribution): 10–60 minutes

t ½ (terminal): approximately 2–5 days

The considerable protein binding of the total platinum contents results in an extended or incomplete excretion phase with cumulative urine secretion ranging from 27 to 45% of the administered dose in a period from 84 to 120 hours. An extended infusion results in the urine secretion of a larger part of the dose. The faecal secretion is minimal, and small amounts of platinum can be traced in the gallbladder and the large intestine. Dysfunctional kidneys increase the plasma half-life period, which may also increase theoretically in the presence of ascites caused by the highly protein binding activities of cisplatin.

5.3 Preclinical safety data

Chronic toxicity:

Chronic toxicity models indicate kidney damage, bone marrow depression, gastro-intestine disorders and ototoxicity.

Mutagenity and carcinogenity:

Cisplatin is mutagenic in numerous in vitro and in vivo tests (bacterial test systems and chromosome defects in animal cells and tissue cultures). Long term studies of cisplatin on mice and rats evidenced the carcinogenic effects.

Reproductive toxicity:

Fertility: Gonadal suppression resulting in amenorrhoea or azoospermia may be irreversible and cause definitive infertility.

Pregnancy and lactation: Cisplatin is embryotoxic and teratogenic for mice and rats, and defects have been reported for both species. Cisplatin was found in the milk.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Sodium chloride, hydrochloric acid 10% m/m, water for injections.

6.2 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 in section 6.6.

The cisplatin 0.5mg/ml concentrate 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 in section 6.6.

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

6.3 Shelf life

2 years

After dilution (see section 6.6. and 6.4.): 24 hours

6.4 Special precautions for storage

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

After dilution (see section 6.6.):

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for solutions with a final cisplatin concentration of 0.1mg/ml after dilution of the cisplatin 0.5mg/ml 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 dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of the container

Amber Type 1 glass vial (20ml, 50ml, 100ml) with chlorobutyl rubber stopper with aluminium overseal.

1 vial containing 10mg/20ml of cisplatin.

1 vial containing 25mg/50ml of cisplatin.

1 vial containing 50mg/100ml of cisplatin.

6.6 Instructions for use and handling and disposal

Cisplatin "Ebewe" 0.5mg/ml concentrate for solution for infusion 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 (see section 6.2.).

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 concentrate 0.5mg/ml calculated according to the instructions in section 4.2. should be diluted in 1–2 litres of one of the above mentioned solutions.

The diluted solution should be administered only by intravenous infusion (see section 4.2.).

Only clear and colourless solutions without visible particles should be used.

For single use only.

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).

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

7. MANUFACTURER

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