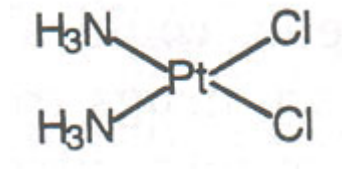


NEW ZEALAND

CISPLATIN EBEWE[®] cisplatin 100 mg/100 mL Injection

Name of the Medicine

Cisplatin



Molecular formula: Cl₂H₆N₂Pt

Molecular weight: 300.06

CAS: 15663-27-1

Description

Cisplatin is a yellow to orange crystalline powder that is slightly soluble in water.

Cisplatin Ebewe (cisplatin solution) is a clear colourless sterile aqueous solution of cisplatin 1.0mg/mL in vials containing 10mg, 50mg or 100mg cisplatin for intravenous administration.

Uses

Actions

Cisplatin Ebewe has biochemical properties similar to that of bifunctional alkylating agents producing interstrand and intrastrand crosslinks in DNA. It is apparently cell-cycle non-specific.

Pharmacokinetics

Following a single I.V. dose, cisplatin concentrates in liver, kidneys, and large and small intestines in animals and humans. Cisplatin apparently has poor penetration into the CNS. Plasma levels of radioactivity decay in a biphasic manner after an I.V. bolus dose of radioactive cisplatin to patients.

Following bolus injection of intravenous infusion over 2 to 7 hours, of doses ranging 50 to 100 mg/m², plasma cisplatin half-life is approximately 30 minutes. The ratios of cisplatin to total, free (ultrafilterable) platinum in the plasma range from 0.5 to 1.1 after a dose of 100 mg/m².

Cisplatin does not undergo instantaneous and reversible binding to plasma proteins characteristic of normal medicine-protein binding; however, the platinum from cisplatin

becomes bound to plasma proteins. These complexes are slowly eliminated with a half-life of 5 days or more.

Over a range of doses administered as bolus injections or infusions of up to 24 hours, approximately 10 to 40% of the platinum administered is excreted in the urine in 24 hours. Similar mean urinary recoveries of platinum are found following daily administration on five consecutive days. Intact cisplatin accounts for the majority of platinum excreted in the urine within one hour of administration. Renal clearance of cisplatin exceeds creatinine clearance. The renal clearance of free (ultrafilterable) platinum also exceeds creatinine clearance, is non-linear and depends on dose, urine flow rate and individual variability in tubular secretion and reabsorption. No close correlation exists between the renal clearance of either free (ultrafilterable) platinum or cisplatin and creatinine clearance. Mannitol administration increases urinary excretion of Cisplatin Ebewe following intravenous infusion and excretion of up to 75% in 24 hours has been reported. There is a potential for accumulation of free (ultrafilterable) platinum in plasma when cisplatin is administered on a daily basis, but not when it is administered on an intermittent basis.

Although small amounts of platinum are present in the bile and large intestine after administration of cisplatin, faecal excretion of platinum appears to be insignificant.

Indications

Cisplatin Ebewe is indicated as palliative therapy to be employed as follows:

Metastatic Non-seminomatous Germ Cell Carcinoma:

In established combination therapy with other approved chemotherapeutic agents in patients with metastatic non-seminomatous germ cell tumours who have already received appropriate surgical and/or radiotherapeutic procedures.

Metastatic Ovarian Tumours:

Cisplatin Ebewe, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumours refractory to standard chemotherapy who have not previously received Cisplatin Ebewe therapy.

Advanced and Refractory Carcinoma of the Bladder:

Cisplatin Ebewe, as a single agent, is indicated as secondary therapy in patients with advanced stage bladder cancer refractory to standard chemotherapy who have not previously received Cisplatin Ebewe therapy.

Squamous Cell Carcinoma of the Head and Neck (Refractory to Standard Chemotherapy):

Cisplatin Ebewe, as a single agent, is indicated as secondary therapy in patients with squamous cell carcinoma of the head and neck refractory to standard chemotherapy who have not previously received Cisplatin Ebewe therapy.

Dosage and Administration

Note:

Needles or intravenous sets containing aluminium parts that may come in contact with Cisplatin Ebewe should not be used for preparation or administration. Aluminium reacts with Cisplatin Ebewe, causing precipitate formation and a loss of potency.

The solution should be used intravenously only and should be administered by I.V. infusion only as recommended below.

Metastatic Non-seminomatous Germ Cell Carcinoma:

The usual dosage of Cisplatin Ebewe for the treatment of non-seminomatous carcinoma in combination with other approved therapeutic agents is :

20mg/m² I.V. daily for 5 days (Days 1-5) every three weeks for three courses.

Metastatic Ovarian Tumours:

As a single agent, Cisplatin Ebewe may be administered at a dose of 100mg/m² I.V. once every 4 weeks.

Advanced and Refractory Carcinoma of the Bladder:

Cisplatin Ebewe should be administered as a single agent at a dose of 50-70 mg/m² I.V. once every 3 to 4 weeks depending on the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m² repeated every 4 weeks is recommended.

Squamous Cell Carcinoma of the Head and Neck (Refractory to Standard Chemotherapy):

As a single agent, Cisplatin Ebewe may be administered at a dose of 100mg/m² I.V. once every 4 weeks.

The following important principles should be taken into consideration when administering cisplatin:

1. Cisplatin must be administered in an intravenous solution containing at least 0.3 percent NaCl. This amount of chloride ion is essential to maintain cisplatin stability in intravenous solution. The medicine should be diluted in Sodium Chloride Intravenous Infusion (0.9%) or in 1/2 or 1/3 physiologic saline with 5 percent Glucose.
2. A urine output of 100 mL/hr or greater will tend to minimise cisplatin nephrotoxicity. This can be accomplished by prehydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 mL/m²/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g. mannitol).
3. Cisplatin doses of 60 mg/m² have been administered safely over 1-2 hours; doses greater than 60 mg/m² should be administered over 6-8 hours with sufficient fluid to maintain adequate urine output during administration and post administration.

4. Cisplatin administration has been associated with electrolyte imbalances including symptomatic hypomagnesaemia. Therefore monitoring of serum electrolytes, before, during and after every course of cisplatin is recommended.

A repeat course of Cisplatin Ebewe should not be given until the serum creatinine is below 1.5 mg/100 mL and/or the BUN is below 25 mg/100 mL. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets \geq 100,000/mm³, WBC \geq 4,000/mm³). Subsequent doses of Cisplatin Ebewe should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

Contraindications

Cisplatin Ebewe is contraindicated in patients with pre-existing renal impairment. Cisplatin Ebewe should not be employed in myelosuppressed patients, in patients who are dehydrated and those with pre-existing renal impairment or patients with hearing impairment.

Cisplatin Ebewe is contraindicated in patients with a history of allergic reactions to Cisplatin Ebewe or other platinum-containing compounds.

Cisplatin is nephrotoxic and neurotoxic (in particular ototoxic). These toxicities may be cumulative if disorders of this type pre-exist.

Patients receiving cisplatin should not breastfeed.

Concurrent administration of yellow fever vaccine is contraindicated.

Warnings and Precautions

Cisplatin Ebewe should be administered only in a hospital under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

As with other platinum-based products, hypersensitivity reactions appearing in most cases during perfusion may occur, and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (See **Contraindications** and **Adverse Effects**).

Cisplatin produces cumulative nephrotoxicity. The serum creatinine, BUN, and creatinine clearance should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, Cisplatin Ebewe should not be given more frequently than once every 3 to 4 weeks (see **Adverse Effects**). This can be accomplished by pre-hydration with 2 liters of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 mL/m²/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (eg, mannitol).

Anaphylactic-like reactions to cisplatin have been reported and include facial oedema bronchostriction, tachycardia and hypotension. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of adrenaline, corticosteroids and antihistamines.

There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of cisplatin or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. A neurologic examination must be carried out at regular intervals

Loss of motor function has also been reported.

Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of medicine (see **Adverse Effects**). Cisplatin has been found to have a carcinogenic potential in animals. The development of acute leukaemia co-incident with the use of cisplatin has been reported rarely in humans. In these reports, cisplatin was generally given in combination with other leukaemogenic agents.

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurological examination should also be performed regularly (see **Adverse Effects**).

Neurologic examination should also be performed regularly (see **Adverse Effects**). Cisplatin Ebewe should be administered only in a hospital under the supervision of a qualified physician experienced in the use of cancer chemotherapy agents.

Because of its high protein binding Cisplatin Ebewe may interfere with the distribution of other protein bound medications.

As cisplatin produces cumulative nephrotoxicity and ototoxicity, other nephrotoxic or ototoxic medicines should be avoided during cisplatin therapy unless unavoidable.

Following dilution of the solution Cisplatin Ebewe undergoes varying degrees of decomposition, depending on the diluent used. Normal Saline is the preferred diluent (see **Dosage and Administration**).

Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during medicine administration. A specific treatment for extravasation reactions is unknown at this time.

Use in pregnancy: (Category D)

Cisplatin Ebewe, like several other cytotoxic agents, is likely to produce foetal damage. Safe use in human pregnancy has not been established. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice cisplatin is teratogenic and embryotoxic.

During treatment with cisplatin and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy; this applies to patients of both genders.

Genetic counseling 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 treatment.

Use in lactation:

Cisplatin is excreted in breast milk.

To avoid possible harm to the baby, breast feeding is not advised during Cisplatin Ebewe therapy.

Effects on ability to drive and use machines. No studies on the effects on ability to drive and use machines have been performed. Nevertheless, the profile of undesirable effects (like nephrotoxicity) may influence the ability to drive vehicles and use machinery.

Adverse Effects

Renal and urinary disorders:

Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of 50mg/m². It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe (sometime fatal) with high or repeated courses of the medicine. Renal function must return to normal before another dose of Cisplatin Ebewe can be given. Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6 to 8 hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilisation of these procedures.

Ear and labyrinth disorders:

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50mg/m², and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation and may be related to peak plasma concentration of cisplatin. Careful monitoring or audiometry should be performed prior to initiation of therapy and prior to subsequent doses of Cisplatin Ebewe. Vestibular toxicity has also been reported.

Blood and lymphatic system disorders:

Myelosuppression occurs in 25 to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50mg/m²). Anaemia (decrease of >2g haemoglobin/100mL) occurs at approximately the same frequency but with a later onset than leukopenia and thrombocytopenia.

Cisplatin has been shown to sensitise red blood cells, sometimes resulting in a direct Coombs-positive haemolytic anaemia. The incidence, severity and relative importance of this effect in relation to other haematological toxicity has not been established, but the possibility of a haemolytic process should be considered in any person who is receiving Cisplatin Ebewe and has an unexplained fall in haemoglobin. The haemolytic process reverses on cessation of therapy.

The development of acute leukemia coincident with the use of cisplatin has been reported rarely in humans. In these reports, cisplatin was generally in combination with other leukemogenic agents.

Gastrointestinal disorders:

This cytostatic agent has a more marked toxicity than is usually found in antineoplastic chemotherapy.

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the medicine must be discontinued. Nausea and vomiting usually begin within one to four hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to one week after treatment.

Delayed nausea and vomiting (beginning or persisting 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy.

Diarrhoea has also been reported.

These side effects are only partially relieved by standard antiemetics. Rare occurrence of stomatitis has been reported.

Nervous system disorders:

Peripheral neuropathies occur infrequently with usual doses of the medicine. They are generally sensory in nature (e.g. paraesthesia of the upper and lower extremities), but can also include motor difficulties, reduced or absent reflexes and leg weakness. Autonomic neuropathy, seizures, slurred speech, loss of taste and memory loss have also been reported. These neuropathies usually appear after prolonged therapy, but have also developed after a single medicine dose. Areflexia and loss of proprioception and vibratory sensation may be seen, especially if cisplatin is given at higher doses or more frequently than recommended. In some patients they may be irreversible however, they have been partially or completely reversible in others following discontinuance of cisplatin therapy. Cerebrovascular accident has been reported in patients treated with cisplatin. Convulsions, leukoencephalopathy and reversible posterior leukoencephalopathy syndrome have been rarely reported. Muscle cramps of sudden onset and short duration have been reported. These were usually reported in patients who had received a relatively high dose of cisplatin, and who had a relatively advanced stage of peripheral neuropathy.

Metabolism and nutritional disorders:

Hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokalaemia and hypophosphataemia have been reported to occur in patients with cisplatin and are probably related to renal tubular damage. Tetany has occasionally been reported in those patients with hypocalcaemia and hypomagnesaemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin.

Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricaemia has been reported to occur at approximately the same frequency as the increase in BUN and serum creatinine. It is more pronounced after doses greater than 50mg/m², and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricaemia effectively reduces uric acid levels.

Eye disorders:

Optic neuritis, papilloedema and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established.

Blurred vision and altered colour perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended. The altered colour perception manifests as a loss of colour discrimination, particularly in blue-yellow axis. The only finding on fundoscopic examination is irregular retinal pigmentation of the macular area.

Immune system disorders:

Anaphylactic-like reactions have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial oedema, wheezing, tachycardia and hypotension within a few minutes of medicine administration. Reactions may be controlled by intravenous adrenalin, corticosteroids and antihistamines. Patients receiving Cisplatin Ebewe should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatobiliary disorders:

Transient elevations of hepatic enzymes, and bilirubin can occur when Cisplatin Ebewe is administered in recommended doses.

Cardiac disorders: Cardiovascular abnormalities (e.g. coronary disease, congestive heart failure, arrhythmias, postural hypotension, thrombotic microangiopathy).

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary toxicity has been reported in patients treated with cisplatin in combination with bleomycin or 5-fluorouracil.

Skin and Subcutaneous Tissue Disorders: Mild alopecia. Rarely, urticarial or maculopapular skin rashes have also been observed.

Musculoskeletal and Connective Tissue Disorders: Myalgia.

Reproductive System and Breast Disorders:

Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported. Although the impairment of spermatogenesis can be reversible, males undergoing cisplatin treatment should be warned about the possible adverse effects on male fertility.

Neoplasm benign, malignant, and unspecified: Acute leukemia has been reported as occurring uncommonly.

Infections and infestations: Sepsis is commonly observed.

General Disorders and Administration Site Conditions: Pyrexia occurs very commonly. Local effects such as phlebitis, cellulitis and skin necrosis (following extravasation of the medicine) may also occur.

Other Toxicities:

Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogenous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesaemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesaemia, or a combination of any of these factors.

Interactions with other medicines

Plasma levels of anticonvulsants may become subtherapeutic during cisplatin therapy.

In a randomised trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used with Altretamine (hexamethylmelamine) and cisplatin.

The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients who have previously been given cisplatin.

Ifosfamide may increase hearing loss due to cisplatin.

Oral anticoagulants. In the event of simultaneous use of oral anticoagulants, it is advisable regularly to check the INR.

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

Attenuated live vaccines. Live vaccines should not be used in patients undergoing Cisplatin therapy. Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease (see **CONTRAINDICATIONS**). In view of the risk of generalized illness, it is advisable to use an inactivated vaccine if available.

Overdosage

Contact the Poisons Information Centre on 0800 POISON or 0800 764766 for advice on management of overdose.

Caution should be used to prevent inadvertent overdosage with Cisplatin Ebewe.

Acute overdosage with this medicine may result in kidney failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, intractable nausea and vomiting and/or neuritis. In addition, death can occur following overdosage.

No proven antidotes have been established for cisplatin overdosage. Haemodialysis even when initiated four hours after overdosage, appears to have little effect on removing platinum

from the body because of rapid and high degree of protein binding of cisplatin. Management of overdosage should include general supportive measures to sustain the patient through the period of toxicity that may occur.

Pharmaceutical Precautions

Cisplatin Ebewe: Store between 15°C to 25°C. Do not refrigerate. Protect from light. The recommended storage of unopened vials provides a stable product until the expiration date on the label.

Solutions of Cisplatin Ebewe: Cisplatin Ebewe diluted to 0.10 mg/mL in either 0.9% sodium chloride, 1:1 mixture of 5% glucose and 0.9% sodium chloride or a 1:1 mixture of 5% mannitol and 0.9% sodium chloride is chemically stable for 24 hours when stored at room temperature (25°C) and protected from light.

Cisplatin Ebewe is for single use in one patient only. Contains no antimicrobial agent. Discard any unused residue.

Procedures for Handling and Disposal of Anticancer Medicines:

Procedures for proper handling and disposal of anti-cancer medicines should be considered. Several guidelines on this subject have been published and should be used appropriately.

As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of Cisplatin Ebewe. Skin reactions associated with accidental exposure to Cisplatin Ebewe may occur. The use of gloves is recommended. If Cisplatin Ebewe solution contacts skin or mucosae, immediately wash the skin or mucosae thoroughly with soap and water.

Conforming to the procedures appropriate for the manipulation and elimination of cytostatic agents is recommended.

Before administering the solution to the patient, verify the clarity of the solution and the absence of particles.

Presentation and Storage Conditions

| | |
|-----------------|--------------------------------|
| Cisplatin Ebewe | 100mg in 100mL glass vial; 1's |
| | 50mg in 50mL glass vial; 1's |
| | 10mg in 10mL glass vial; 1's |

Store at or below 25°C. Protect from light. Do not refrigerate.

Medicine Classification

Prescription Medicine (S4)

Further Information

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central atom of platinum surrounded by two chlorine atoms and two ammonia molecules in the cis position. The molecular formula of the active ingredient is $\text{PtCl}_2\text{H}_6\text{N}_2$, with a molecular weight of 300.1. It is soluble in water or saline at 1mg/mL and in dimethylformamide at 24mg/mL.

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Date of Preparation

16 August 2011