齐鲁制药有限公司
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Contact: Ms. Han Guilin
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IMPORTANT PRESCRIBING INFORMATION

May 24, 2023

Subject: Temporary Importation of CISplatin Injection with non-U.S. Labeling to Address Drug Shortage

Dear Healthcare Professional,

Due to the critical shortage of CISplatin Injection in the United States (U.S.), Qilu Pharmaceutical Co. Ltd (Qilu), in conjunction with Apotex Corp., is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of the drug. Qilu has initiated temporary importation of CISplatin Injection (50 mg/50 mL) with vial and carton labels in Chinese into the U.S. market. The CISplatin Injection from Qilu is marketed and manufactured in China and is not FDA-approved.

Only Qilu or its distributor, Apotex Corp., is authorized by the FDA to import or distribute Qilu's CISplatin Injection in the United States.

Effective immediately and during this temporary period, Apotex Corp. will distribute the following presentation of CISplatin Injection to address the critical shortage:

Product Name	**Quantity**	**Description**	**U.S. NDC Number**	**Lot Number**	**Expiration Date**
CISplatin Injection (50 mg/50 mL)	1 vial per carton	Colorless to yellowish clear liquid Each 1 mL contains 1 mg of CISplatin and 9 mg of Sodium Chloride in water for injection.	60505-6277-0 **The linear barcode on the imported product label may not register accurately on the U.S. scanning systems** See Appendix 1 for scannable linear barcode	3E001C88	05/02/2025
				3E002C88	05/02/2025
				3E003C88	05/02/2025
				3E004C88	05/03/2025

It is important to note the following:

- The carton labeling and container label did not include the warning statements, "Stop! Verify Drug Name and Dose!" or "CISplatin doses greater than 100 mg/m^2 once every 3 to 4 weeks are rarely used". Thus, a sticker containing this warning statement, the name of the product, strength, concentration, U.S. NDC number and linear barcode has been applied to the vial and the carton.
- The container label did not have the translated name of the product "CISplatin". Thus,

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a sticker containing the information noted in the bullet above has been applied to the vial.

- Drug- drug interaction with bisulfite, metabisulfite, sodium bicarbonate and fluorouracil.
- The product is colorless to yellowish clear liquid.
- The vial and carton labels will display the text used and approved for marketing the products in China containing Chinese only text. Example images of this labeling are provided in Appendix 2.
- There are differences in the format and content of the labeling between the FDA-approved product and Qilu's CISplatin Injection. Please see the product comparison table in Appendix 3 and corresponding English translations.

CISplatin injection is available only by prescription in the U.S. The imported lots did not have the statement "Rx only" on their labeling. Thus, a sticker containing the information noted in the bullet above has been applied to the vial and the carton.

The linear barcode on the imported product label may not register accurately on the U.S. scanning systems. Institutions should manually input the imported product information, including the NDC, into their systems and confirm that the linear barcode, if scanned, provides correct information. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

In addition, the carton of the imported product does not include a product identifier as required under the Drug Supply Chain Security Act (DSCSA). Specifically, each package of product does not include the NDC, unique serial number, lot number, and expiration date in both human-readable form and a two-dimensional data matrix barcode.

Please refer to the package insert for the FDA-approved CISplatin Injection drug product for full prescribing information.

Finally, please ensure that your staff and others in your institution who may be involved in the administration of CISplatin Injection receive a copy of this letter and review the information.

If you have any questions about the information contained in this letter, any quality related problems, or questions on the use of Qilu's CISplatin Injection, please contact Apotex Corp. Customer Service at 1-800-706-5575.

For ordering information, please contact your primary wholesaler or distributor to place an order with Apotex Corp. at 1-800-706-5575.

Healthcare providers should report adverse events associated with the use of Qilu's CISplatin Injection to Apotex Corp. at 1-800-706-5575.

Adverse events or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail, or by fax:

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- Complete and submit the report Online: www.fda.gov/medwatch/report.htm
- Regular mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178.

We remain at your disposal to answer any questions you may have about our product; and provide more information if needed.

Sincerely,

Mr. Yin Xunliao
Deputy General Manager
Qilu Pharmaceutical Co., Ltd.

Enclosures:
Appendix 1 – Barcodes for Pharmacy Dispensing
Appendix 2 – Product Label and Product Characteristics Side-by-Side Comparison Table
Appendix 3 – Prescribing Information Side-by-Side Comparison Table
Available at www1.apotex.com/us/CISplatin Injection

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Appendix 1: Barcode for Pharmacy Dispensing

Product Name	**Quantity**	**Linear Barcode**
CISplatin Injection (50 mg/50 mL)	1 vial per carton	 A sticker containing this linear barcode has been applied to the vial and the carton.

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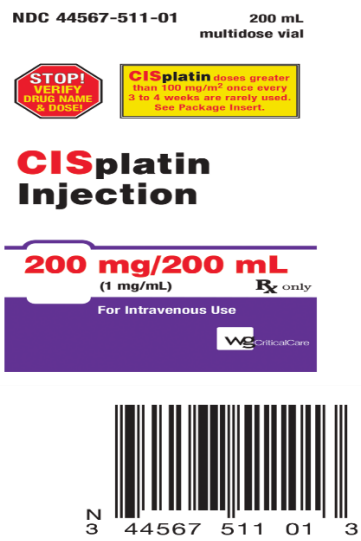
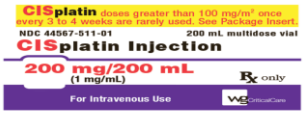
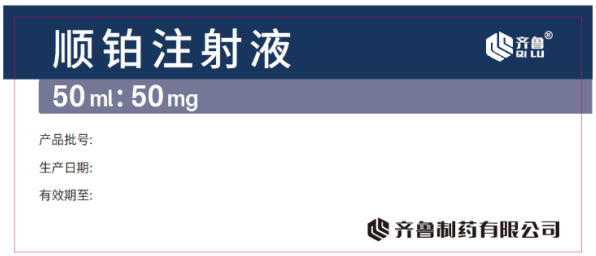
Appendix 2: Product Label and Product Characteristics Side-by-Side Comparison Table

	U.S. FDA Approved Product	Imported Product
Carton Labeling		
Vial Label	  	
Product Name	CISplatin Injection	CISplatin Injection
Route of Administration	Intravenous injection	Intravenous injection
Ingredients	CISplatin Injection infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL or 100 mL amber vial of infusion concentrate contains: 1 mg/mL CISplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0,	The main ingredient of this product is CISplatin. Excipients: sodium chloride, dilute hydrochloric acid, sodium hydroxide and water for injection Colorless to yellowish clear liquid Each 1 mL contains 1 mg CISplatin and 9 mg of Sodium Chloride in water for injection

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	and water for injection to a final volume of 50 mL or 100 mL, respectively.	
Storage Conditions	Store at 15° C to 25°C (59° to 77°F). Do not refrigerate. Protect unopened container from light. The CISplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.	Store at 15-25°C, protected from light, and avoid refrigeration.

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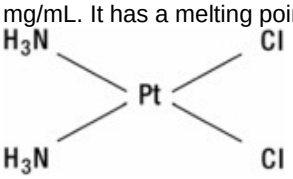
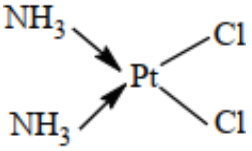
Appendix 3: Prescribing Information Side-by-Side Comparison Table (translated from Chinese)

	U.S. FDA Approved Product	**Imported Product**
Product name	CISplatin Injection	CISplatin Injection
Active Ingredient	CISplatin	CISplatin
Available Strengths / Concentrations	50 mL or 100 mL or 200 mL 1 mg/mL	50 mg/50 mL
Route of Administration	For Intravenous Use	Intravenous infusion Arterial perfusion Intrathoracic and intraperitoneal injection
Ingredients	CISplatin Injection infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL or 100 mL amber vial of infusion concentrate contains: 1 mg/mL CISplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50 mL or 100 mL, respectively. The active ingredient, CISplatin, is a yellow to orange crystalline powder with the molecular formula $PtCl_2H_6N_2$, and a molecular weight of 300.1. CISplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207° C. 	The main ingredient of this product is CISplatin. Chemical name: (Z)-dichlorodiammineplatinum Chemical structural formula:  Molecular formula: $Cl_2H_6N_2Pt$ Molecular weight: 300.05 Excipients: sodium chloride, dilute hydrochloric acid, sodium hydroxide and water for injection.
Warnings	WARNING CISplatin Injection should be administered 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. Cumulative renal toxicity associated with CISplatin is severe. Other major dose-related toxicities are myelosuppression, nausea, and vomiting. Ototoxicity, which may be more pronounced in children, and is manifested by tinnitus, and/or loss of high frequency hearing and occasionally deafness, is significant. Anaphylactic-like reactions to CISplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of CISplatin administration. Epinephrine, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms (see WARNINGS and ADVERSE REACTIONS sections). Exercise caution to prevent inadvertent CISplatin overdose. Doses greater than 100 mg/m^2/cycle once every 3 to 4 weeks are rarely used. Care must be taken to avoid inadvertent CISplatin overdose due to confusion with carboplatin or prescribing practices that fail to	See Precautions and Adverse Reactions sections

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	U.S. FDA Approved Product	Imported Product
	differentiate daily doses from total dose per cycle. CISplatin produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, blood urea nitrogen (BUN), creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, CISplatin should not be given more frequently than once every 3 to 4 weeks (see ADVERSE REACTIONS). Elderly patients may be more susceptible to nephrotoxicity (see PRECAUTIONS, Geriatric Use). 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 ofproprioception and vibratory sensation. Elderly patients may be more susceptible to peripheral neuropathy (see PRECAUTIONS, Geriatric Use). Loss of motor function has also been reported. Anaphylactic-like reactions to CISplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to CISplatin, and have been alleviated by administration of epinephrine, corticosteroids, and antihistamines. CISplatin can commonly cause ototoxicity which is cumulative and may be severe. Audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug (see ADVERSE REACTIONS). All pediatric patients receiving CISplatin should have audiometric testing at baseline, prior to each subsequent dose, of drug and for several years post therapy. CISplatin can cause fetal harm when administered to a pregnant woman. CISplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice CISplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant. The carcinogenic effect of CISplatin was studied in BD IX rats. CISplatin was administered intraperitoneally (i.p.) to 50 BD IX rats for 3 weeks, 3 X 1 mg/kg body weight per week. Four hundred and fifty-five days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma. The development of acute leukemia coincident with the use of CISplatin has been reported. In these reports, CISplatin was generally given in combination with other leukemogenic agents. Injection site reactions may occur during the administration of CISplatin (see ADVERSE REACTIONS). Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this	

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	U.S. FDA Approved Product	Imported Product
	time.	
Indications	CISplatin Injection is indicated as therapy to be employed as follows: Metastatic Testicular Tumors In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures. Metastatic Ovarian Tumors In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of CISplatin Injection and cyclophosphamide. CISplatin Injection, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received CISplatin Injection therapy. Advanced Bladder Cancer CISplatin Injection is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments, such as surgery and/or radiotherapy.	CISplatin Injection is indicated for the palliative treatment of small cell and non-small cell lung cancer, non-seminomatous germ cell cancer, advanced refractory ovarian cancer, advanced refractory bladder cancer, refractory head and neck squamous cell carcinoma, gastric cancer and esophageal cancer. It may be used as a single agent or in combination with other chemotherapeutic agents and, where appropriate, combined with other treatments such as radiotherapy and surgery.
Dosage and Administration	CISplatin Injection is administered by slow intravenous infusion. CISPLATIN INJECTION SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION. Note: Needles or intravenous sets containing aluminum parts that may come in contact with CISplatin Injection should not be used for preparation or administration. Aluminum reacts with CISplatin Injection, causing precipitate formation and a loss of potency. Metastatic Testicular Tumors The usual CISplatin Injection dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/ m^2 IV daily for 5 days per cycle. Metastatic Ovarian Tumors The usual CISplatin Injection dose for the treatment of metastatic ovarian tumors in combination with cyclophosphamide is 75 to 100 mg/ m^2 IV per cycle once every four weeks (DAY 1). The dose of cyclophosphamide when used in combination with CISplatin Injection is 600 mg/ m^2 IV once every 4 weeks (DAY 1). For directions for the administration of cyclophosphamide, refer to the cyclophosphamide package insert. In combination therapy, CISplatin Injection and cyclophosphamide are administered sequentially. As a single agent, CISplatin Injection should be administered at a dose of 100 mg/ m^2 IV per cycle once every four weeks. Advanced Bladder Cancer CISplatin Injection should be administered as a single agent at a dose of 50 to 70 mg/ m^2 IV per cycle 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	Adults: This product should be diluted with 1 liter of sodium chloride injection for infusion. This product is slightly viscous. In order to make the dosage accurate, inject appropriate amount of sodium chloride injection into the bottle after sucking out the solution, shake the bottle slightly so as to suck out the solution adhered to the inner wall of the bottle, then add it into the infusion bottle. Intravenous infusion: 20 mg/m^2 based on body surface area, once daily for 5 consecutive days; or 30 mg/m^2, once daily for 3 consecutive days, repeated for 3-4 courses at an interval of 3 weeks; or 80-100 mg/m^2 once every 3-4 weeks along with hydration therapy and diuresis. Arterial perfusion: 40-50 mg/m^2 once every 4 weeks when combined with interventional chemotherapy, with hydration and diuresis required. Intrathoracic and intraperitoneal injection. 30-60 mg once Pediatric use: For monotherapy, the following two doses are recommended: 50-120 mg/m^2 once every 3-4 weeks; 15-20 mg/m^2/d for 5 consecutive days, repeated every 3-4 weeks; For combination chemotherapy, the recommended dose is 20 mg/m^2 or higher every 3-4 weeks, but not more than the dose for CISplatin monotherapy. According to the weight of the child, this product should be diluted with appropriate amount of sodium chloride injection for infusion. Precautions: 1. Pre-treatment hydration: Patients should

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	U.S. FDA Approved Product	Imported Product
	dose of 50 mg/ m^2 per cycle repeated every 4 weeks is recommended. All Patients Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a CISplatin Injection dose is recommended. The drug is then diluted in 2 liters of 5% Dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol, and infused over a 6-to 8-hour period. If diluted solution is not to be used within 6 hours, protect solution from light. Do not dilute CISplatin Injection in just 5% Dextrose Injection. Adequate hydration and urinary output must be maintained during the following 24 hours. A repeat course of CISplatin Injection 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 $\geqslant$100,000/mm^3, WBC≥4000/mm^3). Subsequent doses of CISplatin Injection should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.	receive adequate hydration prior to and within 24 hours of CISplatin administration to ensure good urinary output and to minimize nephrotoxicity. Hydration may be intravenously given with 2 liters of 0.9% sodium chloride intravenous infusion or dextrose saline (e.g., 4% dextrose in 1/5 of 0.9% sodium chloride) over 2 hours. During the last 30 minutes of hydration prior to administration or after hydration, 375 mL of 10% Mannitol Injection may be infused through the lateral arm. 2. Treatment: CISplatin is infused (1-2 hours) immediately after pre-treatment hydration, and infusions up to 6-8 hours have been hypothesized to reduce gastrointestinal and nephrotoxicity. The IV bottle should be covered to protect from light. 3. Post-treatment hydration: Adequate hydration and urine output must be maintained for 24 hours after intravenous drip. Continued intravenous hydration is recommended after treatment. The goal is to administer 2 liters of 0.9% sodium chloride or dextrose saline with intravenous infusion over a period of 6-12 hours.
Preparation of Intravenous Solutions	Preparation Precautions Caution should be exercised in handling the aqueous solution. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing CISplatin. Skin reactions associated with accidental exposure to CISplatin may occur. The use of gloves is recommended. If CISplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water. More information is available in the references listed below. Instructions for Preparation The aqueous solution should be used intravenously only and should be administered by IV infusion over a 6-to 8-hour period (see DOSAGE AND ADMINISTRATION). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. NOTE TO PHARMACIST: Exercise caution to prevent inadvertent CISplatin overdosage. Please call prescriber if dose is greater than 100 mg/ m^2 per cycle. Aluminum and flip-off seal of vial have been imprinted with the following statement: CALL DR. IF DOSE>100 MG/ m^2/CYCLE.	Adults: This product should be diluted with 1 liter of sodium chloride injection for infusion. This product is slightly viscous. In order to make the dosage accurate, inject appropriate amount of sodium chloride injection into the bottle after sucking out the solution, shake the bottle slightly so as to suck out the solution adhered to the inner wall of the bottle, then add it into the infusion bottle. Pediatric use: According to the weight of the child, this product should be diluted with appropriate amount of sodium chloride injection for infusion.
Adverse Reactions	Nephrotoxicity Dose-related and cumulative renal insufficiency, including acute renal failure, 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 50 mg/ m^2. 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 with repeated courses of the drug. Renal function must return	Cumulative and dose-related renal impairment is the major dose-limiting toxicity of CISplatin. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. The administration of CISplatin using a 6- to 8-hour infusion with intravenous hydration, and mannitol can lower the incidence and severity of nephrotoxicity. Ear and labyrinth disorders Tinnitus and/or loss of high frequency hearing has been observed in up to 31% of patients treated with CISplatin. Ototoxicity, which may be more

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	U.S. FDA Approved Product	Imported Product
	to normal before another dose of CISplatin can be given. Elderly patients may be more susceptible to nephrotoxicity (see PRECAUTIONS, Geriatric Use). 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 utilization of these procedures. Ototoxicity Ototoxicity has been observed in up to 31% of patients treated with a single dose of CISplatin 50 mg/ m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). The prevelance of hearing loss in children is particularly high and is estimated to be 40-60%. Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of CISplatin has been reported. 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 CISplatin doses. It is unclear whether CISplatin-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the peak plasma concentration of CISplatin. Ototoxicity can occur during treatment or be delayed. Audiometric monitoring should be performed prior to initiation of therapy, prior to each subsequent dose, and for several years post therapy. The risk of ototoxicity may be increased by prior or simultaneous cranial irradiation, and may be more severe in patients less than 5 years of age, patients being treated with other ototoxic drugs (e.g. aminoglycosides and vancomycin), and in patients with renal impairment. Genetic factors (e.g. variants in the thiopurine S-methyltransferase [TPMT] gene) may contribute to CISplatin-induced ototoxicity; although this association has not been consistent across populations and study designs. Hematologic 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 (>50 mg/ m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression (see PRECAUTIONS, Geriatric Use). In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of CISplatin hemolytic anemia, a further	pronounced in children, is more common and more severe with repeated doses. Ocular system disorders Blurred vision, colour blindness acquired, cortical blindness, optic neuritis, papilledema, retinal pigmentation. Infections and infestations Infection (death due to complications of infection), sepsis Neoplasms benign, malignant and unspecified Secondary malignancy and acute leukemia are known to occur. Blood and lymphatic system disorders Thrombotic microangiopathy (hemolytic-uremic syndrome), bone marrow hematopoietic failure, neutropenia, thrombocytopenia, leukopenia, anemia, Coombs' positive hemolytic anemia. Leukopenia and thrombocytopenia are dose-dependent and are more pronounced at doses over 50 mg/m^2. The nadir of platelet and white blood cell decline generally occurs on days 18-32 of treatment (range 7.3-45), with most patients recovering on day 39 (range 13-62). Anemia occurs at approximately the same frequency. Immune system disorders Anaphylactic-like reactions have been reported in patients previously exposed to CISplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Other CISplatin-related adverse reactions that have been reported rarely include cardiac abnormality, SGOT increased and liver injury. It is known that the patient may develop secondary malignancy and acute leukemia. Infusion of solutions with a CISplatin concentration greater than 0.5 mg/mL may result in extravasation. Endocrine disorders Inappropriate antidiuretic hormone (secretion) syndrome is known to occur. Metabolism and nutrition disorders CISplatin may cause patients to experience the following reactions: hyponatremia, hypomagnesemia, dehydration, hypokalemia, hypophosphatemia, hyperuricemia, hypocalcemia, and tetany. Nervous system disorders Convulsions, peripheral neuropathy, leukoencephalopathy, reversible posterior leukoencephalopathy syndrome, cerebrovascular accident, hemorrhagic stroke, ischemic stroke, loss of taste, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy. Cardiac disorders Arrhythmia, bradycardia, tachycardia, myocardial infarction, asystole, cardiac abnormality. Vascular system disorders Raynaud's phenomenon.

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	course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of CISplatin has been reported. In these reports, CISplatin was generally given in combination with other leukemogenic agents. Gastrointestinal Marked nausea and vomiting occur in almost all patients treated with CISplatin, and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of CISplatin therapy. Diarrhea has also been reported. To report SUSPECTED ADVERSE REACTIONS, contact WG Critical Care, LLC at 1-866-5624708 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. OTHER TOXICITIES Vascular toxicities coincident with the use of CISplatin in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic-uremic syndrome [HUS]), 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 hypomagnesemia 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, hypomagnesemia, or a combination of any of these factors. Serum Electrolyte Disturbances Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with CISplatin and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing CISplatin. Inappropriate antidiuretic hormone syndrome has also been reported. Hyperuricemia Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/ m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose.	Venous thromboembolism A significantly increased risk of venous thrombotic events has been reported in patients with advanced solid tumors treated with CISplatin compared to non-CISplatin-based chemotherapy. Vascular toxicities coincident with the use of CISplatin in combination with other antineoplastic agents have rarely been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident (hemorrhagic and ischemic stroke), thrombotic microangiopathy (hemolytic-uremic syndrome), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. Respiratory, thoracic and mediastinal disorders Pulmonary embolism. Gastrointestinal disorders Stomatitis, vomiting, nausea, anorexia, hiccups, diarrhea. Marked nausea and vomiting occur in almost all patients treated with CISplatin. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 1 week after treatment. Skin and subcutaneous tissue disorders Rash, alopecia. Musculoskeletal and connective tissue disorders Muscle cramps. Renal and urinary disorders Acute renal failure, renal failure, renal tubular disorder. Reproductive system and breast disorders Anomalies of spermatogenesis. General disorders and administration site conditions Fever, asthenia, discomfort, injection site extravasation (extravasation may result in local soft tissue toxicity including tissue cellulitis, fibrosis, necrosis, pain, edema, erythema). Some patients have sensory and motor neurotoxicity, usually characterized by peripheral neuropathies. Myelosuppression may occur in patients treated with CISplatin. Hyperuricemia may occur in patients receiving CISplatin. It is mainly due to drug-induced nephrotoxicity. It is more pronounced after doses greater than 50 mg/ m^2, and peak levels generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels. Hypomagnesemia and hypocalcemia may occur after CISplatin treatment or drug withdrawal. Hypomagnesemia and hypocalcemia may characterized by muscle stress or cramps, clonus, tremors, carpopedal spasms or conic convulsions. Serum electrolyte levels should be monitored regularly and supplemented when necessary.

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	Allopurinol therapy for hyperuricemia effectively reduces uric acid levels. Neurotoxicity See WARNINGS. Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of CISplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of CISplatin. CISplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy (see PRECAUTIONS, Geriatric Use). Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) have also been reported. Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of CISplatin and with a relatively advanced symptomatic stage of peripheral neuropathy. Ocular Toxicity Optic neuritis, papilledema, and cerebral blindness have been reported 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 color perception have been reported after the use of regimens with higher doses of CISplatin or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area. Anaphylactic-Like Reactions Anaphylactic-like reactions have been reported in patients previously exposed to CISplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving CISplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication. Hepatotoxicity Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with CISplatin administration at the recommended	

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	doses. Other Events Cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, asthenia, and dehydration have been reported. Local soft tissue toxicity has been reported following extravasation of CISplatin. Severity of the local tissue toxicity appears to be related to the concentration of the CISplatin solution. Infusion of solutions with a CISplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.	
Contraindications	CISplatin is contraindicated in patients with preexisting renal impairment. CISplatin should not be employed in myelosuppressed patients, or in patients with hearing impairment. CISplatin is contraindicated in patients with a history of allergic reactions to CISplatin or other platinum-containing compounds.	CISplatin is contraindicated in patients with a history of allergic reactions to CISplatin or other platinum-containing compounds, in pregnant or nursing women, and in patients with renal impairment. CISplatin should not be employed in patients with hearing impairment, or in myelosuppressed patients.
Precautions	Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly (see ADVERSE REACTIONS).	CISplatin should only be used in patients who are experienced in anticancer therapy. Patients with liver impairment: Studies in humans have demonstrated that CISplatin is highly uptake in the liver. Aspartate aminotransferase (AST) elevations have been reported in some cases, therefore the adult dose must be used carefully, and liver function must be monitored periodically. Neurologic examination should also be performed regularly. Patients with renal impairment: CISplatin shows high tissue uptake in the kidney, and is mainly excreted by the kidney, with potential dose-related cumulative renal toxicity. The most common change in renal function is a decrease in glomerular filtration rate, which can be reflected by an increase in serum creatinine. Therefore, blood urea nitrogen (BUN), serum creatinine and creatinine clearance must be measured and renal function must return to acceptable limits before the start of treatment with CISplatin or before the next course of treatment. It is recommended to use CISplatin every 3-4 weeks. Hydration is recommended to reduce renal toxicity. In addition, the plasma elimination half-life is prolonged in patients with renal failure. CISplatin should be used with caution in patients with pre-existing renal impairment and should be contraindicated in patients with serum creatinine levels > 0.2 mmol/L. Multiple repeated courses of treatment are not approved until the serum creatinine level is not less than 0.14 mmol/L or the blood urea nitrogen level is not less than 9 mmol/L. Ototoxicity The CISplatin-induced ototoxicity is cumulative and audiometric testing should be performed before the start of treatment if conditions permit, and performed periodically thereafter especially

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		if clinical symptoms such as tinnitus or poor hearing occur. Radiotherapy may worsen ototoxicity. Tinnitus or occasional hearing loss to normal tones is an indication of ototoxicity, which is often observed. Hearing test abnormalities are more common, and hearing loss may be unilateral or bilateral, may increase in occurrence frequency and severity with repeated drug administrations and may be irreversible, but occur most often in the range of 4,000 to 8,000 Hz. Myelosuppression Myelosuppression may occur in patients treated with CISplatin. Leukopenia and thrombocytopenia are more pronounced at doses > 50 mg/m^2, and andanemia (hemoglobin decrease > 2 g%) is roughly the same in incidence as leukopenia and thrombocytopenia, but generally occurs later. A subsequent course of treatment with CISplatin should not be started until platelets > 100,000/mm^3 and leukocytes > 4,000/mm^3 are achieved. A high incidence of severe anemia requiring transfusion of packed red blood cells has been observed in patients receiving CISplatin-containing combination chemotherapy. Rarely, CISplatin may cause hemolytic anemia: positive direct Coomb's test results have been reported in a few of these cases. Periodic peripheral blood counting must be performed during treatment with CISplatin. Anaphylaxis Anaphylaxis has occasionally been reported when patients who have been exposed to CISplatin in the past are retreated with CISplatin. Patients with a history or family history of allergy are at a particular risk of anaphylaxis. Facial edema, sneezing, tachycardia, hypotension, and urticaria-like nonspecific maculo-papular rashes may occur within minutes after the injection. Severe reactions can be controlled with epinephrine, adrenal cortical hormones, and antihistamines. Patients receiving CISplatin must be carefully observed to prevent anaphylactic-like reactions, and the use of CISplatin must be accompanied by supportive equipment and medications to treat such complications. Cardiovascular toxicity CISplatin has been found to be associated with cardiovascular toxicity (see [Adverse Reactions]). Patients may present with clinically diverse venous thrombotic events, myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, and cerebral arteritis. Cases of pulmonary embolism, including fatalities, have been reported (see [Adverse Reactions]). Hypomagnesemia and hypocalcemia With CISplatin, hypomagnesemia is fairly frequent, whereas hypocalcemia occurs less frequently. Loss of magnesium is often

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		accompanied by renal tubular damage, which prevents the reabsorption of magnesium ions. Lack of the both electrolytes may lead to convulsions, which don't appear to be dose-related. Electrolyte monitoring is necessary. Neurotoxicity and convulsions Peripheral neuropathy, postural hypotension, and convulsions may occur with CISplatin, which seems to be common after prolonged administration, and the further use of CISplatin should generally be contraindicated in patients with significant clinical symptoms. Others: As there are increased risks of bleeding, bruising and infection in patients treated with CISplatin, it is recommended to exercise extreme caution in implementing the necessary invasive operations. Due to the risk of gastrointestinal bleeding with CISplatin, drinking alcohol and taking aspirin should be avoided. CISplatin should be used with extreme caution if a patient has had a recent infection, particularly varicella and herpes zoster. Live virus vaccines should not be used in patients receiving CISplatin. Dental department: The myelosuppressive effects of CISplatin may lead to an increased incidence of microbial infections, delayed wound healing and gingival bleeding. Dental procedures should be avoided during CISplatin therapy.
Drug Interactions	Plasma levels of anticonvulsant agents may become subtherapeutic during CISplatin therapy. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and CISplatin.	Drugs that may be nephrotoxic or ototoxic, such as aminoglycoside antibiotics and diuretics, may enhance the nephrotoxicity and ototoxicity of CISplatin. Incompatibilities: CISplatin can interact with aluminum to form a black precipitate. Needles, syringes, cannulas or intravenous sets containing aluminium must not be used when preparing or administering CISplatin. The presence of bisulfite, metabisulfite, sodium bicarbonate and fluorouracil can affect the stability of CISplatin.
Carcinogenesis, Mutagenesis, Impairment of Fertility	See WARNINGS. Pregnancy Pregnancy Category D See WARNINGS. Nursing Mothers CISplatin has been reported to be found in human milk; patients receiving CISplatin should not breast-feed. Pediatric Use Safety and effectiveness in pediatric patients have not been established. All children should have audiometric monitoring performed prior to initiation of therapy prior to each subsequent dose, and for several years post therapy. Advanced testing methods may allow for earlier detection of hearing loss in an attempt to facilitate the rapid initiation of interventions that can limit the potential adverse impact of hearing impairment on a child's cognitive and social development.	[Use in Pregnant and Lactating Women] CISplatin is mutagenic in bacteria and produces chromosome aberrations in mammalian cells. In mice, CISplatin was teratogenic and embryotoxic. CISplatin may cause genitourinary toxicity to the fetus. Patients should be advised to avoid becoming pregnant while using this medicinal product. CISplatin has been reported to appear in human milk; Patients receiving CISplatin should not breastfeed. [Pediatric Use] Safety and efficacy of this product in pediatric patients have not been established. All children should have hearing monitoring prior to each subsequent start of dosing and for several years after treatment. Advanced testing

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	Geriatric Use Insufficient data are available from clinical trials of CISplatin in the treatment of metastatic testicular tumors or advanced bladder cancer to determine whether elderly patients respond differently than younger patients. In four clinical trials of combination chemotherapy for advanced ovarian carcinoma, 1484 patients received CISplatin either in combination with cyclophosphamide or paclitaxel. Of these, 426 (29%) were older than 65 years. In these trials, age was not found to be a prognostic factor for survival. However, in a later secondary analysis for one of these trials, elderly patients were found to have shorter survival compared with younger patients. In all four trials, elderly patients experienced more severe neutropenia than younger patients. Higher incidences of severe thrombocytopenia and leukopenia were also seen in elderly compared with younger patients, although not in all CISplatin-containing treatment arms. In the two trials where nonhematologic toxicity was evaluated according to age, elderly patients had a numerically higher incidence of peripheral neuropathy than younger patients. Other reported clinical experience suggests that elderly patients may be more susceptible to myelosuppression, infectious complications, and nephrotoxicity than younger patients. CISplatin is known to be substantially excreted by the kidney and is contraindicated in patients with preexisting renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.	methods can detect hearing loss earlier, allowing more rapid interventions to reduce the potential adverse effects of hearing loss on cognitive and social development in children. [Geriatric Use] CISplatin is known to be substantially excreted by the kidney and is contraindicated in patients with pre-existing renal injury. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection when using them, and their renal function should be monitored.
Overdosage	Caution should be exercised to prevent inadvertent overdosage with CISplatin. Acute overdosage with this drug 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. Hemodialysis, even when initiated four hours after the overdosage, appears to have little effect on removing platinum from the body because of CISplatin's rapid and high degree of protein binding. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that may occur.	In the event of overdose or toxic reactions, symptomatic treatment or supportive measures must be taken. Patients must be monitored for 3-4 weeks. To prevent delayed toxicity.
Pharmacology and Toxicology	Plasma concentrations of the parent compound, CISplatin, decay monoexponentially with a half-life of about 20 to 30 minutes following bolus administrations of 50 or 100 mg/ m^2 doses. Monoexponential decay and plasma half-lives of about 0.5 hour are also seen following 2-hour or 7-hour infusions of 100 mg/ m^2. After the latter, the total-body clearances and volumes of distribution at steady-state for CISplatin are about 15 to 16 L/h/ m^2 and 11 to 12 L/ m^2. Due to its unique chemical structure, the chlorine atoms of CISplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme-catalyzed metabolism. At	Pharmacological action The main mechanism of the cytotoxic action involves the binding of CISplatin to genomic DNA in the cell nucleus to form interstrand and intrastrand cross-links. This interferes with normal transcription and/or DNA replication mechanisms and triggers cytotoxic processes that lead to cell death. Toxicological studies Genotoxicity CISplatin Ames test and mammalian cell chromosome aberration test were positive. Reproductive toxicity

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	physiological pH in the presence of 0.1M NaCl, the predominant molecular species are CISplatin and monohydroxymonochloro cis-diammine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by sulfhydryl groups of amino acids or proteins, accounts for the instability of CISplatin in biological matrices. The ratios of CISplatin to total free (ultrafilterable) platinum in the plasma vary considerably between patients and range from 0.5 to 1.1 after a dose of 100 mg/m^2. CISplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-protein binding. However, the platinum from CISplatin, but not CISplatin itself, becomes bound to several plasma proteins, including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three-hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from CISplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or more. Following CISplatin doses of 20 to 120 mg/ m^2, the concentrations of platinum are highest in liver, prostate, and kidney; somewhat lower in bladder, muscle, testicle, pancreas, and spleen; and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Platinum is present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentrations in tumors are generally somewhat lower than the concentrations in the organ where the tumor is located. Different metastatic sites in the same patient may have different platinum concentrations. Hepatic metastases have the highest platinum concentrations, but these are similar to the platinum concentrations in normal liver. Maximum red blood cell concentrations of platinum are reached within 90 to 150 minutes after a 100 mg/ m^2 dose of CISplatin and decline in a biphasic manner with a terminal half-life of 36 to 47 days. Over a dose range of 40 to 140 mg CISplatin/ m^2 given as a bolus injection or as infusions varying in length from 1 hour to 24 hours, from 10% to about 40% of the administered platinum is excreted in the urine in 24 hours. Over five days following administration of 40 to 100 mg/ m^2 doses given as rapid, 2-to 3-hour, or 6-to 8-hour infusions, a mean of 35% to 51% of the dosed platinum is excreted in the urine. Similar mean urinary recoveries of platinum of about 14% to 30% of the dose are found following five daily administrations of 20, 30, or 40 mg/ m^2/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. Platinum-containing species excreted in the urine are the same as those found following the incubation of CISplatin with urine from healthy subjects, except that the proportions are different. The parent compound, CISplatin, is excreted in the urine and accounts for 13% to 17% of the dose excreted	Teratogenic effects were observed in animals injected with CISplatin during and after organogenesis. A published mouse study showed placental transfer was observed in animals treated with CISplatin, and it was increased with placental maturation. Carcinogenicity Carcinogenicity studies of CISplatin injection were conducted on BDIX rats. CISplatin was administered intraperitoneally (i.p.) to 50 BDIX rats for 3 weeks, 3 X 1 mg/kg body weight per week. 455 days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma.

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	within one hour after administration of 50 mg/ m^2. The mean renal clearance of CISplatin exceeds creatinine clearance and is 62 and 50 mL/min/ m^2 following administration of 100 mg/ m^2 as 2-hour or 6-to 7-hour infusions, respectively. The renal clearance of free (ultrafilterable) platinum also exceeds the glomerular filtration rate indicating that CISplatin or other platinum-containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear and variable and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption. There is a potential for accumulation of ultrafilterable platinum plasma concentrations whenever CISplatin is administered on a daily basis but not when dosed on an intermittent basis. No significant relationships exist between the renal clearance of either free platinum or CISplatin and creatinine clearance. Although small amounts of platinum are present in the bile and large intestine after administration of CISplatin, the fecal excretion of platinum appears to be insignificant.	
Pharmacokinetics		CISplatin uptake was very good in kidney, liver and intestine. More than 90% of the plasma platinum was protein bound (possibly irreversibly). Total platinum is rapidly eliminated from plasma within 4 hours after intravenous administration, followed by a slower elimination phase due to covalent binding to serum proteins. Plasma levels of unbound platinum declined with a half-life of 20 minutes to 1 hour and were dependent on the rate of drug infusion. Elimination of unchanged drug and of various platinum-containing biotransformation products was excreted via urine. Within 2-4 hours of intravenous administration of CISplatin, 15-25% of platinum was rapidly eliminated, with most of the early excretion being unchanged drug, and 20-80% excreted in the first 24 hours, the remaining was drug bounded to tissue or plasma proteins.
Storage	CISplatin Injection is a sterile, multidose vial without preservatives. Store at 15° C to 25°C (59° to 77°F). Do not refrigerate. Protect unopened container from light. The CISplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.	Store at 15-25 ℃, protected from light, and avoid refrigeration. [Packaging] Borosilicate moulded glass injection vials and chlorobutyl rubber stopper for injection coated with PTFE/ HFP copolymer film, 1 vial/box. [Shelf Life] 24 months