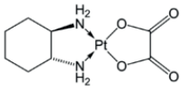
OXALIPLATINO KEMEX
OXALIPLATIN 50 mg - 100 mg
Lyophilized Injectable
Route of Administration: Intravenous

Made in Argentina | Under prescription only

QUALI-QUANTITATIVE COMPOSITION:
OXALIPLATINO KEMEX 50 mg
Each vial contains:
Oxaliplatin.....50 mg
Lactose monohydrate.....450 mg
OXALIPLATINO KEMEX 100 mg
Each vial contains:
Oxaliplatin.....100 mg
Lactose monohydrate.....900 mg

THERAPEUTIC ACTION
Antineoplastic agent.
ATC Classification: L01XA03

Structural and Molecular Formula: $C_8H_{14}N_2O_4Pt$



INDICATIONS
Oxaliplatin, in combination with 5-fluorouracil (5-FU) and folinic acid (AF), is indicated for:
-Adjuvant treatment of stage III (Dukes' stage C) colon cancer following complete resection of the primary tumor,
-Treatment of metastatic colorectal cancer.

PHARMACOLOGICAL ACTION / PROPERTIES
Pharmacological Action
Oxaliplatin is an antineoplastic drug belonging to a new class of platinum compounds in which the platinum atom forms a complex with a 1,2-diaminocyclohexane (DACH) and an oxalate group.
Oxaliplatin is a unique enantiomer, (SP-4-2)-[(1R,2R)-cyclohexane-1,2-diamine-kN, kN'] [ethanedioate(2-)-kO1, kO2] platinum.
Oxaliplatin exhibits a broad spectrum of in vitro cytotoxic activity and in vivo antitumor activity in various tumor model systems, including human colorectal cancer models.
Oxaliplatin also demonstrates in vitro and in vivo activity in various cisplatin-resistant models.
A synergistic cytotoxic action with 5-fluorouracil has been observed both in vitro and in vivo.
Studies on the mechanism of action of oxaliplatin, although not fully elucidated, show that the resulting aqueous derivatives of oxaliplatin interact with DNA, forming intra- and interstrand cross-links, which result in the disruption of DNA synthesis, leading to cytotoxic and antitumor activity.
Pharmacokinetic Properties
The pharmacokinetic parameters of the individual active compounds have not been determined.
The pharmacokinetic parameters of platinum ultrafiltrate, representing a mixture of all unbound, active and inactive platinum species, following a 2-hour infusion of oxaliplatin at 130 mg/m2 every three weeks for 1 to 5 cycles, and oxaliplatin at a dose of 85 mg/m2 every two weeks for 1 to 3 cycles, are as follows:

Table 1: Summary of Platinum Pharmacokinetic Parameter Estimates in an Ultrafiltrate following Multiple Doses of Oxaliplatin at 85 mg/m² every two weeks or 130 mg/m² every three weeks.

Dose	$C_{máx}$ (µg/ml)	AUC_{0-48} (µg.h/ml)	AUC (µg.h/ml)	$T_{1/2}\alpha$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	Vss (l)	Cl (l/h)
85 mg/m²	0.814	4.19	4.68	0.43	16.8	391	440	17.4
Mean ± SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35
130 mg/m²	1.21	8.20	11.9	0.28	16.3	273	582	10.1
Mean ± SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

The average values of AUC_{0-48} and C_{max} were calculated in Cycle 3 (85 mg/m²) or Cycle 5 (130 mg/m²).
The average values of AUC, Vss, Cl, and Cl_{R0-48} were calculated in Cycle 1.
The values of C_{final}, C_{max}, AUC, AUC_{0-48}, Vss, and Cl were determined using non-compartmental analysis.
The values of $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$ were determined using compartmental analysis (combined Cycles 1-3).

At the end of a 2-hour infusion, 15% of the administered platinum is found in the systemic circulation, and the remaining 85% is rapidly distributed in tissues or eliminated through urine. Irreversible binding to erythrocytes and plasma results in half-lives that are close to the natural turnover of erythrocytes and albumin. No accumulation was observed in the plasma ultrafiltrate after the administration of doses of 85 mg/m² every two weeks or 130 mg/m² every three weeks, and steady state was achieved in Cycle 1. Inter- and intra-individual variability is generally low.
In vitro biotransformation is believed to occur through a non-enzymatic degradation process, and there is no data indicating that the diaminocyclohexane (DACH) ring undergoes cytochrome P450-mediated metabolism.
Oxaliplatin undergoes extensive biotransformation in patients, and no unchanged drug was detected in the plasma ultrafiltrate at the end of a 2-hour infusion. Several cytotoxic biotransformation products have been identified in the systemic circulation, including mono-, di-, and diacuo-DACH platinum forms, along with various inactive conjugates at later evaluation time points.
Platinum is predominantly excreted in the urine and is primarily eliminated within 48 hours after administration.
On the fifth day, a significant decrease in clearance, from 17.6 ± 2.18 L/h to 9.95 ± 1.91 L/h, along with a statistically significant decrease in volume of distribution, from 330 ± 40.9 to 241 ± 36.1 L, was observed. The effect of severe renal impairment on plasma clearance has not been evaluated.
The effect of renal dysfunction on the pharmacokinetics of oxaliplatin was studied in patients with varying degrees of renal dysfunction. Oxaliplatin was administered at a dose of 85 mg/m² to patients in the reference group with normal renal function (Clcr > 80 mL/min, n = 12), and to patients with mild renal dysfunction (Clcr = 50-80 mL/min, n = 13) and moderate renal dysfunction (Clcr = 30-49 mL/min, n = 11), and at a dose of 65 mg/m² to patients with severe renal dysfunction (Clcr < 30 mL/min, n = 5).
The median exposure was 9, 4, 6, and 3 cycles, respectively, and pharmacokinetic data were obtained in Cycle 1 in 11, 13, 10, and 4 patients, respectively.
An increase in platinum plasma ultrafiltrate (UFP) AUC and AUC per dose, and a reduction in total and renal elimination and V_{ss}, were observed with increasing renal dysfunction, especially in the (small) group of patients with severe renal dysfunction: the point estimate (95% CI) of the mean ratios calculated by renal status compared to normal renal function for AUC per dose were 1.36 (1.08, 1.71), 2.34 (1.82, 3.01), and 4.81 (3.49, 6.64) in patients with mild, moderate, and severe renal dysfunction, respectively.
Oxaliplatin elimination is significantly related to creatinine clearance.
Platinum UFP elimination was 0.74 (0.59, 0.92) in patients with mild renal dysfunction, 0.43 (0.33, 0.55) in patients with moderate renal dysfunction, and 0.21 (0.15, 0.29) in patients with severe renal dysfunction, and V_{ss} was 0.52 (0.41, 0.65) in patients with mild renal dysfunction, 0.73 (0.59, 0.91) in patients with moderate renal dysfunction, and 0.27 (0.20, 0.36) in patients with severe renal dysfunction.
Therefore, total body elimination of platinum UFP was reduced by 26% in patients with mild renal dysfunction, 57% in patients with moderate renal dysfunction, and 79% in patients with severe renal dysfunction compared to patients with normal renal function.
Renal elimination of platinum UFP was reduced by 30% in patients with mild renal dysfunction, 65% in patients with moderate renal dysfunction, and 84% in patients with severe renal dysfunction compared to patients with normal renal function.
An increase in the β half-life of platinum UFP was detected with increasing degree of renal dysfunction, mainly in the severe renal dysfunction group. Despite the small number of patients with severe renal dysfunction, these data are important for patients with severe renal impairment and should be considered when prescribing oxaliplatin to patients with renal dysfunction.

DOSAGE/ADMINISTRATION
Adults only
The recommended dose of oxaliplatin for adjuvant treatment is 85 mg/m² intravenously, administered every 2 weeks for 12 cycles (6 months). The recommended dose of oxaliplatin for metastatic colorectal cancer treatment is 85 mg/m² intravenously, repeated every 2 weeks. The dose should be adjusted based on drug tolerance.
Oxaliplatin should always be administered before Fluoropyrimidines (5-FU).
Oxaliplatino Kemex is administered as an intravenous infusion lasting 2 to 6 hours, in 250-500 ml of a 5% glucose solution (50 mg/ml), resulting in a concentration between 0.20 mg/ml and 0.70 mg/ml. In clinical practice, the highest concentration for a dose of 85 mg/m² oxaliplatin is 0.70 mg/ml. Oxaliplatin has been primarily used in combination with continuous infusion 5-fluorouracil. For the bi-weekly treatment regimen, bolus 5-fluorouracil and continuous infusion were used.
Reconstitution of the solution
The solvents that can be used to reconstitute the solution are water for injections or a 5% glucose solution.
- For a 50 mg vial: add 10 ml to 20 ml of solvent to obtain an Oxaliplatin concentration of 2.5 to 5.0 mg/ml.
- For a 100 mg vial: add 20 ml to 40 ml of solvent to obtain an Oxaliplatin concentration of 2.5 to 5.0 mg/ml.
From a microbiological and chemical standpoint, the reconstituted solution should be immediately diluted with a 5% glucose solution.
Visually inspect before use. Only transparent solutions without particles should be used.
Dilution prior to infusion
Extract the necessary amount of reconstituted concentrated solution from the vial(s) and dilute it with 250 to 500 ml of a 5% glucose solution to obtain an oxaliplatin concentration of not less than 0.20 mg/ml. Administer the solution by IV infusion.
The solution has been shown to be chemically and physically stable for 24 hours at 2-8ºC.
From a microbiological perspective, this infusion preparation should be used immediately. If not, the storage times during use and the pre-use conditions are the responsibility of the user and should generally not exceed 24 hours at 2-8ºC unless dilution has taken place under controlled and validated aseptic conditions.
This medication is for single use. Any unused solution should be discarded.
Never use sodium chloride solutions or solutions containing chlorides for dilution.
Risk populations
- Renal insufficiency:
Oxaliplatin should not be administered to patients with severe renal dysfunction.
The recommended dose of oxaliplatin for patients with mild to moderate renal dysfunction is 85 mg/m².
- Hepatic insufficiency:
In a phase I study that included patients with various levels of hepatic impairment, the frequency and severity of hepatobiliary disorders appeared to be related to disease progression and baseline impaired liver function tests. During the clinical development phase, no specific dose adjustment was made for patients with impaired liver function tests.
- Elderly patients:
There was no increase in severe toxic effects when oxaliplatin was used as a single agent or in combination with 5-fluorouracil in patients over 65 years of age. Therefore, no specific dose adaptation is required for elderly patients.
- Pediatric patients:
There is no indication for the use of oxaliplatin in children. The effectiveness of oxaliplatin as a single agent in pediatric populations with solid tumors has not been established.

CONTRAINDICATIONS
Oxaliplatin is contraindicated in patients who have:
- Hypersensitivity to oxaliplatin or any of the excipients.
- Women who are breastfeeding.
- Myelosuppression prior to starting the first treatment cycle, as evidenced by neutrophils <2 x 10^9/L and/or a platelet count <100 x 10^9/L.
- Sensory peripheral neuropathy with functional impairment prior to starting the first treatment cycle.
- Severe renal impairment (creatinine clearance less than 30 mL/min).

WARNINGS
Oxaliplatin reacts with metallic aluminum and forms a black platinum precipitate. Needles, catheters, syringes, and all materials for intravenous administration containing aluminum should be avoided during the administration of oxaliplatin.
The use of oxaliplatin should be restricted to specialized oncology units and should be administered under the supervision of an experienced clinical oncologist. Due to limited information available regarding its safety in patients with moderate renal impairment, administration should be considered only after a thorough assessment of the benefit/risk for the patient. In this situation, renal function should be closely monitored, and the dose adjusted based on toxicity.
Patients with a history of allergic reactions to platinum compounds should be closely monitored for possible allergy symptoms. In the event of anaphylactic-like manifestations to oxaliplatin, the infusion should be immediately discontinued, and appropriate symptomatic treatment initiated. Re-administration of oxaliplatin is contraindicated in these patients.
In the case of oxaliplatin extravasation, the infusion should be immediately discontinued, and local symptomatic treatment applied.
Neurological toxic effects of oxaliplatin should be carefully monitored, especially when co-administered with other drugs that have inherent neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.
Patients who develop acute laryngopharyngeal dysaesthesia during the infusion or within 2 hours afterward should receive the next oxaliplatin infusion after 6 hours.
In the event of neurological symptoms (paresthesia, dysaesthesia), the following dose adjustment of oxaliplatin is recommended based on the duration and severity of these symptoms:
- If the symptoms last for more than seven days and are bothersome, the next dose of oxaliplatin should be reduced from 85 to 65 mg/m² (metastatic cancer treatment) or to 75 mg/m² (adjuvant treatment).
- If paresthesia without functional impairment persists until the next cycle, the next dose of oxaliplatin should be reduced from 85 to 65 mg/m² (metastatic cancer treatment) or to 75 mg/m² (adjuvant treatment).
- If paresthesia with functional impairment persists until the next cycle, the treatment should be discontinued.
- If an improvement in symptoms is observed upon discontinuation of treatment, consideration may be given to resuming treatment.
Patients should be informed about the possibility of experiencing persistent symptoms of peripheral sensory neuropathy after completing treatment. Moderate localized paresthesias or paresthesias that may interfere with the patient's functional activities may persist for up to 3 years after completion of adjuvant treatment.
Gastrointestinal toxicity, manifested as nausea and vomiting, justifies prophylactic and/or curative antiemetic treatment.
The presence of severe diarrhea/vomiting can lead to paralytic ileus, gastrointestinal obstruction, dehydration, hypokalemia, metabolic acidosis, and renal failure, especially when oxaliplatin is combined with 5-fluorouracil.
If hematological toxicity occurs (neutrophils <1.5 x 10^9/L or platelets <50 x 10^9/L), the administration of the next treatment cycle should be postponed until hematological values return to acceptable levels. A complete blood count with differential leukocyte count should be performed before starting treatment and before each new treatment cycle.
Patients should be properly informed about the risk of experiencing diarrhea/vomiting, mucositis/stomatitis, and neutropenia following the administration of oxaliplatin and 5-fluorouracil so that they can urgently contact their prescribing physician for appropriate measures.
If mucositis/stomatitis, with or without neutropenia, occurs, the next treatment should be delayed until mucositis/stomatitis recovers to grade 1 or lower and/or until the neutrophil count is ≥1.5 x 10^9/L.
When oxaliplatin is administered with 5-fluorouracil (with or without folinic acid), the inherent toxicity of 5-fluorouracil will result in the usually recommended dose adjustments for this product.
If grade 4 diarrhea (WHO), grade 3-4 neutropenia (neutrophils <1.0 x 10^9/L), or grade 3-4 thrombocytopenia (platelets <50 x 109/L) occur, the dose of oxaliplatin should be reduced from 85 mg/m² to the dose of 5-fluorouracil.
In the case of unexplained respiratory symptoms, such as non-productive cough, dyspnea, radiographic pulmonary infiltrates, or crackles, oxaliplatin treatment should be suspended until further investigations rule out interstitial lung disease.
In cases where liver function test results are abnormal or portal hypertension is not clearly due to hepatic metastasis, it should be considered that it may be due to very rare cases of drug-induced hepatic vascular disorders.
Genotoxic effects were observed with oxaliplatin in preclinical studies. Therefore, men receiving oxaliplatin treatment are advised not to conceive for up to 6 months after treatment and to seek advice on sperm preservation before treatment due to the possibility of infertility caused by oxaliplatin treatment, which may be irreversible.
Women should not become pregnant during treatment with oxaliplatin and should use an effective contraceptive method.
Immunosuppressive effects/increased susceptibility to infections: Administration of live vaccines or attenuated live vaccines in immunocompromised patients receiving chemotherapy agents, including oxaliplatin, may result in severe or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving oxaliplatin. Inactivated vaccines may be administered; however, the response to such vaccines may be diminished.
This medicine contains lactose. Patients with hereditary galactose intolerance, Lapp lactase deficiency (observed in certain populations of Lapland), or glucose/galactose malabsorption should not take this medicine.

PRECAUTIONS
Interaction with other drugs and other forms of interaction
In patients who received a single dose of 85 mg/m² of oxaliplatin immediately before the administration of 5-fluorouracil, no modification in the degree of exposure to 5-fluorouracil was observed.
In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following drugs: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.
Fertility, pregnancy, and lactation
To date, there is no information available on the safety of oxaliplatin use in pregnant women. Reproductive toxicity has been observed in animal studies.
Therefore, oxaliplatin is not recommended during pregnancy or in women of childbearing potential who are not using contraceptive measures.
The use of oxaliplatin should only be considered after adequately informing the patient about the risk it poses to the fetus and obtaining her consent.
Appropriate contraceptive measures should be taken during and for 4 months after cessation of treatment for women and 6 months for men.
The excretion of oxaliplatin in breast milk has not been studied. Breastfeeding is contraindicated during treatment with oxaliplatin.
Oxaliplatin may have a negative effect on fertility.
Effects on the ability to drive and use machinery
No studies have been conducted on the effects on the ability to drive and use machinery. However, treatment with oxaliplatin may increase the risk of dizziness, nausea, vomiting, and other neurological symptoms that can affect walking and balance and have a slight or moderate impact on the ability to drive and use machinery.
Visual disturbances, specifically transient vision loss (reversible upon discontinuation of treatment), may occur, which can affect patients' ability to drive and operate machinery. Therefore, patients should be warned about the potential effect of oxaliplatin on their ability to drive or use machinery.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
As with other potentially toxic compounds, precautions should be taken when handling and preparing oxaliplatin solutions.
Handling instructions
The handling of this cytotoxic agent by healthcare personnel or physicians requires the use of all necessary precautions to ensure the protection of the handler and their work area.
The preparation of injectable solutions of cytotoxic agents should be carried out by specialized personnel in the handling of these types of medications, under conditions that guarantee environmental protection and, above all, the protection of the personnel handling these drugs in accordance with the hospital's policy. Preparation should be carried out in a designated area.
Smoking, eating, and drinking should be prohibited in this area.
Personnel should be provided with appropriate materials for handling, including long-sleeved gowns, masks, caps, protective eyewear, sterile single-use gloves, protective suits for the work area, containers, and waste collection bags.
Feces and vomit should be handled with care.
Pregnant women should be advised to avoid handling cytotoxic agents.
Any broken container should be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in properly labeled rigid containers.
If oxaliplatin powder, reconstituted solution, or infusion solution comes into contact with the skin, immediately and thoroughly wash with water.
If oxaliplatin powder, reconstituted solution, or infusion solution comes into contact with mucous membranes, immediately and thoroughly rinse the affected area with water.

Special administration precautions
- DO NOT use injection materials containing aluminum.
- For reconstitution, only water or a 5% glucose solution can be used as diluents.
- DO NOT administer the undiluted reconstituted solution.
- Only a 5% glucose infusion solution should be used as the diluent for infusion. DO NOT dilute with solutions containing sodium chloride or chlorides. In the absence of compatibility studies, DO NOT mix with any other medication in the same infusion bag or administer simultaneously with other medications through the same infusion line.
- DO NOT mix with alkaline solutions or drugs, particularly 5-fluorouracil, folinic acid preparations containing tromethamine as an excipient, and tromethamine salts of other medications. Alkaline medications or their solutions may adversely affect the stability of oxaliplatin.

Instructions for use in combination with folinic acid (such as calcium folinate or disodium folinate)
Administer an IV infusion of 85 mg/m² of oxaliplatin in 250 to 500 ml of 5% glucose solution with an IV infusion of folinic acid in 5% glucose solution over 2 to 6 hours, through a Y-line placed immediately before the injection site.
These two drugs should not be combined in the same infusion bag. Folinic acid should not contain tromethamine as an excipient and should only be diluted with isotonic 5% glucose solutions, never in alkaline or sodium chloride solutions or solutions containing chlorides.
Instructions for use in combination with 5-Fluorouracil
Oxaliplatin should always be administered before fluoropyrimidines, i.e., 5-fluorouracil.
After the administration of oxaliplatin, flush the line and administer 5-fluorouracil.

ADVERSE REACTIONS / SIDE EFFECTS

The most frequently observed adverse reactions of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhea, nausea, vomiting, and mucositis), hematological (neutropenia, thrombocytopenia), and neurological (acute sensory peripheral neuropathy and cumulative dose-related neuropathy).
In general, these adverse reactions were more frequent and severe with the combination of oxaliplatin and 5-FU/FA than with 5-FU/FA alone.
The frequencies described in the following table were extracted from clinical studies conducted in the treatment of metastatic cancer and adjuvant treatment (which included 416 and 1,108 patients, respectively, in the oxaliplatin + 5-FU/FA treatment groups) and post-marketing data.
The adverse reactions are listed in decreasing order of severity within each frequency interval:
Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Frequency not known (cannot be estimated from the available data)
After the table, additional data is provided.

Table 2: Adverse reactions according to the System Organ Class

Classification of organs in the MedDRA system	Very common	Common	Uncommon	Rare	Very rare
Infectious Disorders and Infestations*	Infections	Rhinitis Upper respiratory tract infections Febrile neutropenia neutropenic sepsis			
Blood and Lymphatic System Disorders*	Anemia, Neutropenia, Thrombocytopenia Leucopenia Lymphopenia			Immune-mediated thrombocytopenia Hemolytic anemia	
Immune System Disorders*	Allergy/allergic reactions				
Metabolic and Nutritional Disorders	Anorexia Altered blood glucose levels Hypokalemia Altered sodium levels	Dehydration	Metabolic acidosis		
Psychiatric Disorders		Depression Insomnia	Nervousness		
Nervous System Disorders*	Sensory peripheral neuropathy Sensory disturbances Dysgeusia (distorted sense of taste) Headache	Dizziness Motor neuritis Meningitis		Dysarthria (difficulty in articulating speech)	
Visual Disorders		Conjunctivitis Visual disturbances		Transient visual acuity impairment Visual field abnormalities Optic neuritis	
Ear and Labyrinth Disorders			Ototoxicity	Hearing loss	
Vascular Disorders	Epistaxis (nosebleed)	Hemorrhage Flushing Deep vein thrombosis Pulmonary embolism			
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea (shortness of breath) Cough	Hiccup		Interstitial lung disease Pulmonary fibrosis	
Gastrointestinal Disorders*	Nausea Diarrhea Vomiting Stomatitis/Mucositis (inflammation of the mouth and mucous membranes) Abdominal pain Constipation	Dyspepsia (indigestion) Gastroesophageal reflux Gastrointestinal bleeding Rectal bleeding	Ileus (intestinal obstruction) Intestinal obstruction	*Colitis, including Clostridium difficile-associated diarrhea	
Skin and Subcutaneous Tissue Disorders	Skin disorders Alopecia (hair loss)	Skin exfoliation (e.g., hand-foot syndrome) Erythematous rash Rash Hyperhidrosis (excessive sweating) Nail disorders			
Musculoskeletal and Connective Tissue Disorders	Back pain	Arthralgia (joint pain) Bone pain			
Renal and Urinary Disorders		Dysuria (painful or difficult urination) Altered frequency of urination Hematuria (blood in urine)			Acute tubulointerstitial nephropathy leading to acute renal failure
General Disorders and Administration Site Conditions	Fatigue Fever++ Asthenia Pain Reactions at the administration site				
Investigations	Increased liver enzymes Increased blood alkaline phosphatase Increased blood bilirubin Increased lactate levels Weight gain (in adjuvant treatment)	Increased blood creatinine Weight loss (in metastatic treatment)			

+Adverse allergic reactions such as skin rash (especially urticaria), conjunctivitis, and rhinitis are common.
Frequent anaphylactic reactions, including bronchospasm, chest pain, angioedema, hypotension, and anaphylactic shock.
++Very common fever, chills (shivering), either of infectious origin (with or without febrile neutropenia) or isolated fever of immunological origin.
+++Injection site reactions have been observed, including local pain, redness, swelling, and thrombosis. Extravasation may cause severe local pain and inflammation, leading to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein.

Hepatobiliary disorders:
Very rare (≤ 1/10,000)
Sinusoidal obstruction syndrome of the liver, also known as hepatic veno-occlusive disease or pathological manifestations related to hepatic alterations, including hepatic peliosis, nodular regenerative hyperplasia, and perisinusoidal fibrosis. Clinical manifestations may include portal hypertension and/or increased transaminases.
Renal and urinary disorders:
Very rare (≤ 1/10,000)
Acute tubular necrosis, acute interstitial nephritis, and acute renal failure.
Lymphatic and blood system disorders:

Table 3: Incidence per patient (%) and by grade.

Oxaliplatin and 5-FU/LV 85 mg/m² every 2 weeks	Metastatic cancer treatment			Adjuvant treatment		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Anemia	82.2	3	< 1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	< 1	77.4	1.5	0.2
Febrile neutropenia	5.0	3.6	1.4	0.7	0.7	0.0
Neutropenic sepsis	1.1	0.7	0.4	1.1	0.6	0.4

Gastrointestinal disorders:

Table 4: Incidence per patient (%) and by grade.

Oxaliplatin and 5-FU/LV 85 mg/m² every 2 weeks	Metastatic cancer treatment			Adjuvant treatment		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Nausea	69.9	8	< 1	73.7	4.8	0.3
Diarrhea	60.8	9	2	56.3	8.3	2.5
Vomiting	49.0	6	1	47.2	5.3	0.5
Mucositis/stomatitis	39.9	4	< 1	42.1	2.8	0.1

It is recommended to use prophylaxis and/or treatment with potent antiemetics. The presence of severe diarrhea/vomiting can lead to dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis, and renal failure, especially when oxaliplatin is combined with 5-fluorouracil.

Nervous system:
The dose-limiting toxicity of oxaliplatin is neurological. This results in sensory peripheral neuropathy characterized by dysesthesias and/or paresthesias of the extremities, with or without cramps, often exacerbated by cold. These symptoms occur in up to 95% of treated patients. The duration of the symptoms, which typically decrease between treatment cycles, increases with the number of cycles. The appearance of pain and/or functional impairment requires dose adjustment or even discontinuation of treatment, depending on the duration of the symptoms. This functional impairment, including difficulty in performing delicate movements, is possibly a consequence of sensory alterations. The risk of persistent symptoms is approximately 10% for a cumulative dose of 850 mg/m2 (10 cycles) and 20% for a cumulative dose of 1,020 mg/m2 (12 cycles). In most cases, neurological signs and symptoms improve or completely resolve after discontinuation of treatment. In adjuvant treatment for colon cancer, 6 months after the completion of treatment, 87% of patients had no symptoms or had mild symptoms. After up to 3 years of follow-up, approximately 3% of patients had either persistent moderate-intensity localized paresthesias (2.3%) or paresthesias that could interfere with functional activities (0.5%). Acute neurosensory manifestations have been reported. These manifestations occur within hours of administration and are often triggered by exposure to cold. They usually present as transient paresthesias, dysesthesias, and hypoesthesia. An acute pharyngolaryngeal dysesthesia syndrome, estimated to occur in 1% to 2% of patients, is characterized by subjective sensations of dysphagia or dyspnea/suffocation sensation without objective evidence of respiratory difficulty (absence of cyanosis or hypoxia) or laryngospasm or bronchospasm (absence of stridor or wheezing). Although antihistamines and bronchodilators have been administered in these cases, the symptoms quickly resolve even without treatment. Prolonging the infusion time helps reduce the incidence of this syndrome. Other occasional symptoms have been observed, including jaw spasms/muscle spasms/involuntary muscle contractions/muscle cramps/myoclonus, abnormal coordination/abnormal gait/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain. In addition, cranial nerve dysfunctions associated with the aforementioned effects may occur, and isolated cases such as ptosis, diplopia, hoarseness/dysphonia/hoarseness sometimes described as vocal cord paralysis, abnormal tongue sensation, or dysarthria sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decreased visual acuity, and visual field disturbances may occur. Other neurological symptoms such as dysarthria, loss of deep tendon reflexes, and Lhermitte's sign have been reported during treatment with oxaliplatin. Isolated cases of optic neuritis have also been reported. Seizures of unknown frequency have been reported post-marketing.

Allergic reactions:

Table 5: Incidence per patient (%) and by grade.

Oxaliplatin and 5-FU/LV 85 mg/m² every 2 weeks	Metastatic cancer treatment			Adjuvant treatment		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Allergic reactions/Allergy	9.1	1	< 1	10.3	2.3	0.6

OVERDOSAGE

There is no known antidote for oxaliplatin. In the event of an overdose, exacerbation of adverse reactions can be expected. Monitoring of hematological parameters should be initiated, and symptomatic treatment should be administered.

In case of an overdose, seek immediate medical attention at the nearest hospital or contact poison control centers:
Hospital de Niños Dr. Ricardo Gutiérrez: Tel: (011) 4962-6666/2247
Hospital Pedro de Elizalde: Tel: (011) 4300-2115 / 4362-6063
Hospital Dr. Juan A. Fernández: Tel: (011) 4808-2655
Hospital Dr. A. Posadas: Tel: (011) 4654-6648 / 4658-7777 / 0800-3330160

PRESENTATIONS

Oxaliplatino Kemex 50 mg
Package containing 1 vial
Oxaliplatino Kemex 100 mg
Package containing 1 vial

STORAGE

Store at room temperature below 30°C, protected from light and moisture in its original container.

KEEP OUT OF REACH OF CHILDREN.
FOR ANY DOUBTS, CONSULT YOUR DOCTOR.
Do not use after the expiration date.

"This medication should be used exclusively under medical prescription and should not be repeated without a new medical prescription."

Medicinal Specialty Authorized by the Ministry of Health. Certificate No. 49,654
Manufactured by:
Laboratorio Kemex S.A.
Nazarre 3446/54 - (C1417DXH)
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05151.00

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