Oxaliplatino GP Pharm
Oxaliplatin

GP Pharm

Lyophilized powder for solution for injection.
Via intravenous infusion.
Made in Argentina

Prescription only medicine

Composition
Each OXALIPLATINO GP PHARM 50 mg vial contains
Oxaliplatin ..... 50 mg
Excipients: lactose.

Each OXALIPLATINO GP PHARM 100 mg vial contains
Oxaliplatin ..... 100 mg
Excipients: lactose.

Indications
Oxaliplatin in combination with 5 fluorouracil is indicated for the adjuvant treatment of stage III colon cancer after complete resection of the primary tumor.
Treatment of metastatic rectal colon cancer.
Pharmacological characteristics
Mechanism of action
Oxaliplatin belongs to a new class of platins in which the central platinum atom is surrounded by an oxalate group and a 1-2 diaminocyclohexane in the trans position. Oxaliplatin is a single enantiomer.
Like other platinum derivatives, it acts on DNA by producing alkyl bonds that lead to the formation of inter-chain and intra-chain bridges and inhibit the synthesis and subsequent replication of DNA.
The kinetics of oxaliplatin binding to DNA is fast and occurs in a maximum of 15 minutes, while that of cisplatin is biphasic with a late phase of 4 to 8 hours. In man its presence in leukocytes has been demonstrated 1 hour after treatment. The synthesis by replication and subsequent separation of DNA is thus inhibited in the same way as secondarily the synthesis of RNA and cellular proteins.
Oxaliplatin exhibits a broad spectrum of in vitro cytotoxic activity and in vivo antitumor activity in a variety of tumor model systems including human colorectal cancer models.
Oxaliplatin has antitumor activity on certain lines resistant to cisplatin.
Synergistic cytotoxic action has been observed with 5-fluorouracil in vitro and in vivo.
In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85mg / m² administered every 2 weeks) combined with folinic 5 fluorouracil is reflected in controlled clinical studies.

PHARMACOKINETICS
The pharmacokinetic parameters of the individual active compounds have not been determined. The pharmacokinetic parameters of the platinum ultrafiltrate representing a mixture of all unbound, active and non-active platinum species following a 2 hour infusion of oxaliplatin at 130 mg / m² every three weeks for 1 to 5 cycles and of oxaliplatin in doses 85 mg / m² every two weeks for 1 to 3 cycles with as follows:
Summary of estimation of the pharmacokinetic parameters of platinum in ultrafiltrate after multiple dose analysis of oxaliplatin at 85 mg/m² every two weeks or 130 mg / m² every three weeks

Dose	C_{max} (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)	V_{ss} (L)	CL (L/h)
85 mg/m² Average	0,814	4,19	4,68	0,43	16,8	391	440	17,4
DE	0,193	0,647	1,40	0,35	5,74	406	199	6,35
130 mg/m² Average	1,21	8,20	11,9	0,28	16,3	273	582	10,1
DE	0,10	2,40	4,60	0,06	2,90	19,0	261	3,07

Mean values of AUC 0-48 and C_{max} values were calculated in Cycle 3 (85mg / m²) or in the 130mg / m² cycle.
The mean values of AUC, Vss, Cl and Cl 0-48 Vss and CL were calculated in cycle 1.
The values of Cend, C_{max}, AUC 0-48 Vss and CL were determined by non-compartmental analysis
The $t_{1/2}$ alpha and $t_{1/2}$ beta were determined by compartment analysis (Cycles 1-3 combined)
At the end of the 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% is rapidly distributed in the tissues or is eliminated in the urine. Irreversible binding to red blood cells and plasma proteins leads to half-lives that are close to the natural renewal process of red blood cells and serum albumin. No accumulation has been observed in the plasma ultrafiltrate after the administration of doses of 85 mg / ml every two weeks or 130 mg / ml every three weeks and the steady state was reached in cycle 1 of this matrix when the variability between and between intra-individual exposure to platinum is generally low.
In vitro biotransformation is considered to be the result of non-enzymatic degradation and there is no evidence of any cytochrome P450 mediated biotransformation of diaminocyclohexane.
Oxaliplatin undergoes extensive metabolism and no unchanged drug was detected in the plasma ultrafiltrate at the end of the 2-hour infusion.
The biotransformation of several cytotoxic products including the platinum monochloro, dichloro and diacuo-DACH species have been identified in the systemic circulation along with several inactive conjugates at later times.
Platinum is predominantly excreted in the urine and is essentially eliminated within 48 hours after administration.
By the fifth day, approximately 54% of the total dose is recovered in the urine and less than 3% in the feces.
A significant decrease in clearance from 17.6 ± 2.18 l / h to 9.95 ± 1.91 l / h was observed in patients with renal failure, together with a significant decrease in the volume of distribution from 330 ± 40.9 to 241 ± 36.1 l. The effect of severe renal impairment on platinum clearance has not been evaluated.

PRECLINICAL SAFETY INFORMATION
Oxaliplatin exhibits the general toxicity of platinum complexes in animals. However, no particular organ has been evicenced in the case of animals, apart from the cardiotoxicity observed in the dog. In particular, oxaliplatin does not have the nephrotoxicity of cisplatin or the myelotoxicity of carboplatin.
Oxaliplatin is mutagenic and clastogenic in mammalian cells and produces embryo-fetal toxicity in rats.
Although no carcinogenic studies have been performed, oxaliplatin is probably carcinogenic.

DOSAGE AND ADMINISTRATION
ONLY FOR ADULTS
The recommended dose of oxaliplatin for adjuvant therapy is 85 mg / m² intravenously administered every two weeks for 12 cycles (6 months).
The recommended dose of oxaliplatin for the treatment of metastatic colorectal cancer is 85 mg / m² intravenously and repeated every two weeks. The dose should be adjusted according to tolerance to the drug.
Oxaliplatin must be administered before fluoropyrimidines, for example 5 fluorouracil.
Oxaliplatin is administered as a 2-6 hour intravenous infusion in 250-500 ml of a 5% glucose solution (50 mg / ml) to give a concentration between 0.2 mg / ml and 0.7 mg / ml. In clinical practice the maximum concentration for an oxaliplatin dose of 85 mg / ml is 0.7 mg / ml.
Oxaliplatin has been used mainly in combination with 5-fluorouracil in continuous infusion regimens. For the fortnightly regimen, 5-fluorouracil regimens have been used in which boluses and continuous infusion are combined.
Oxaliplatin is given as an intravenous infusion. The administration of oxaliplatin does not require hyperhydration.
Oxaliplatin diluted in 250 to 500 ml of 5% glucose solution to administer a concentration not lower than a concentration not lower than 0.2 mg / ml will be perfused either by the central venous route or by the peripheral venous route for 2 to 6 hours. The oxaliplatin infusion should always precede that of 5-fluorouracil.
In case of extravasation, it should be stopped immediately.

Risk populations
Renal impairment: Oxaliplatin has not been studied in patients with severe renal impairment.
In patients with moderate renal impairment, treatment should be started at the normally recommended dose.
No special dose adjustment is necessary in patients with mild renal impairment.
Hepatic failure: In a phase I study that included patients with different levels of liver failure, the frequency and severity of hepato-biliary disorders appeared to be related to the development of the disease and to baseline tests of altered liver function during clinical development.
Elderly: No increase in serious toxic effects was observed when oxaliplatin was used as a single agent or in combination with 5 fluorouracil in patients older than 65 years. Therefore no specific dose adjustment is required in elderly patients.
Pediatric patients: Oxaliplatin is not specifically indicated in children. The efficacy of oxaliplatin monotherapy in pediatric populations with solid tumors has not been established.

Instructions for use
Oxaliplatin must be reconstituted and further diluted before use.
You should only use water for injections or 5% glucose as a solvent for reconstitution and only 5% glucose for subsequent dilution of the concentrate.

SPECIAL RECOMMENDATIONS
Do not use injection material containing aluminum.
Do not administer undiluted.
Only a 5% glucose infusion solution (50 mg / ml) should be used as the solvent. For infusion, DO NOT reconstitute or dilute with sodium chloride or chloride-containing solutions.
DO NOT mix with other medications in the same infusion bag or administer simultaneously in the same infusion line.
DO NOT mix with medicines or alkaline solutions, in particular 5 fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other medicines. Alkaline drugs or their solutions will adversely affect the stability of oxaliplatin.
Do not administer directly intravenously.
Do not mix with any other medicine
Any reconstituted solution showing signs of precipitation should be discarded.

FORM OF USE AND INSTRUCTIONS RELATED TO ITS HANDLING
The handling and reconstitution of oxaliplatin require medical personnel to take precautions in its use, essential for any cytotoxic agent.

RECONSTITUTION OF THE SOLUTION
The solvents usable to reconstitute the solution with water for injections or a 5% glucose solution.
OXALIPLATINO GP PHARM 50 mg: Add 10 ml of solvent to obtain a concentration of 5.0 mg / ml.
OXALIPLATINO GP PHARM 100 mg: Add 20 ml of solvent to obtain a concentration of 5.0 mg / ml. From a microbiological and chemical point of view, the reconstituted solution must be diluted immediately with 5% glucose solution.
The reconstituted solution can be stored for 24 hours in the original bottle between 2 to 8ºC.
Visually inspect before use, only clear solutions without particles should be used.
The medicine is for single use only. Any unused solution must be disposed.

DILUTION BEFORE INFUSION
The reconstituted solution is diluted with 250 to 500 ml of 5% glucose solution to administer at an oxaliplatin concentration between not less than 0.2 and 0.7 mg / ml. The concentration range for which physicochemical stability has been demonstrated is 0.2 to 2.0 mg / ml.
Visually inspect before use. Only clear solutions without particles should be used.
It should be administered by intravenous infusion.
The medicine is for single use only. Any unused infusion solution should be disposed of.
NEVER use sodium chloride or chloride solutions for reconstitution or dilution.
From a microbiological point of view, the prepared infusion should be used immediately. Otherwise, the time and conditions of storage prior to use are the responsibility of the user and should not normally exceed 24 hours at a temperature between 2 and 8 ºC unless the dilution has taken place under controlled and validated aseptic conditions. .
Handling and disposal procedures for appropriate materials should be followed for oxaliplatin as for all objects that come into contact with it. These procedures must conform to the current recommendations for the treatment of cytotoxic residues.

WARNINGS
The use of oxaliplatin should be restricted to specialized medical oncology units and should be administered under the supervision of an experienced clinical oncologist.
Due to limited information on safety in patients with moderate renal impairment, administration should be considered only after an adequate benefit / risk assessment for the patient.
In this situation, renal function must be carefully monitored and the dose adjusted according to toxicity. Likewise, it is necessary to monitor patients with a history of allergic reactions to platinum compounds in order to detect possible allergy symptoms. In the event of an anaphylactic-type reaction to oxaliplatin, the infusion should be stopped immediately and the appropriate symptomatic treatment instituted. Re-exposure of the patient to oxaliplatin is contraindicated in these patients.
In the event of oxaliplatin extravasation, the infusion should be interrupted immediately and the usual symptomatic treatment applied in these situations.
The neurological toxicity of oxaliplatin should be the object of particular vigilance, especially in the case of joint administration with drugs that present their own neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter. For patients who develop acute laryngopharyngeal dysesthesia during or within hours of a two-hour infusion, the next administration of oxaliplatin should last for 6 hours.
In the event of neurological symptoms (paresthesia, dysesthesia), the dose of oxaliplatin should be adjusted according to the following recommendations based on the duration and severity of these symptoms.
If the symptoms last more than seven days and are bothersome for the patient, 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 a picture of paresthesia persists without functional deterioration 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 a picture of paresthesia with functional deterioration persists until the next cycle, the administration of oxaliplatin should be interrupted.
If symptoms improve after stopping treatment, resumption of treatment may be considered.
Patients should be informed of the possibility that peripheral neuropathy symptoms persist after completion of treatment. It may occur that a localized paresthesia of a moderate degree or paresthesia that can interfere with the functional activities of the patient persists up to three years after the end of the treatment when this is administered as adjunctive treatment.
The gastrointestinal toxicity of oxaliplatin, which manifests itself in the form of nausea and vomiting, requires the administration of a prophylactic and / or therapeutic antiemetic treatment.
The presence of severe diarrhea / vomiting especially when oxaliplatin is administered in combination with 5-fluorouracil can cause paralytic ileus, gastrointestinal obstruction, dehydration, hypokalemia, metabolic acidosis and renal insufficiency.
In the event of haematological toxicity (neutrophils <1.5x10⁹/l or platelets <50x10⁹/l), the administration of the following treatment cycle will be postponed until the haematological values return to acceptable levels. A complete blood count should be performed with differentiation of leukocytes before starting oxaliplatin treatment and before each new treatment cycle.
Patients should be informed of the risk of presenting diarrhea / vomiting, mucositis / stomatitis, with or without neutropenia, after the administration of oxaliplatin and 5-fluorouracil, so that they can urgently contact the prescribing physician for adequate treatment. If mucositis / stomatitis appears, with or without neutropenia, the next treatment should be interrupted until the mucositis / stomatitis picture improves and reaches a grade 1 or lower and / or until the neutrophil count is> = 1.5 x 10⁹/ l.
When oxaliplatin is administered in combination with 5-fluorouracil (with or without folinic acid), the inherent toxicity of 5-fluorouracil will lead to the dose adjustments usually recommended for this product.
If grade 4 diarrhea (OHMS) appears, grade 3-4 neutropenia. (Neutrophils <1.0x10⁹/ l) or grade 3-4 thrombocytopenia (platelet <50x 10⁹/ l) the dose of oxaliplatin should be reduced from 85 mg / m² to 65 mg / m² (treatment of cancer metastatic) or 75 mg / m² (adjuvant treatment) in addition to reducing the dissipation of 5-fluorouracil.
In the event of unexplained symptoms such as non productive cough, dyspnoea, radiological or crackling pulmonary infiltrates, treatment with oxaliplatin should be discontinued until subsequent pulmonary examinations make it possible to rule out interstitial lung disease.
In the case of abnormal results of liver function tests or portal hypertension that are not the result of liver metastases, it should be considered that purging is due to rare cases of vascular liver disorders induced by other drugs.
Genotoxic effects of oxaliplatin have been observed in preclinical studies. Therefore, male patients treated with oxaliplatin who are not parents are advised during treatment and up to 6 months after its termination and advise them on sperm freezing before treatment because oxaliplatin has antifertility effects that could be irreversible.
Women should not become pregnant while taking oxaliplatin and should use effective contraception.
SPECIAL PRECAUTIONS
- Both disease and treatment can decrease the number of blood cells. It is necessary to carry out regular analyzes in order to have an efficient control of the treatment.
- Peripheral nervous symptoms (laryngo-pharyngeal spasm and cramps) have been verified, particularly when ingesting cold drinks after their administration.

These symptoms usually remit without leaving sequelae. Consequently report any abnormal tingling sensations or pain in the toes or throat to the doctor.
PRECAUTIONS FOR USE
Oxaliplatin should not be handled by pregnant women.
To prevent nausea and vomiting, an associated treatment can be prescribed
If in doubt consult your doctor.

Instructions for use with folinic acid (as calcium folinate or disodium folinate)
Administer at the same time an IV infusion of 85 mg / ml oxaliplatin in 250 to 500 ml of 5% glucose solution (50 mg / ml) with an IV infusion of folinic acid in 5% glucose solution (50mg / ml). ml), for 2 to 6 hours using a Y line located immediately before the infusion site.
These two drugs should not be combined in the same infusion bag.
Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic glucose solution 5%. (50 mg / ml). never in alkaline solutions or sodium chloride solutions or those containing chlorides.

Instructions for use with 5-fluorouracil
Oxaliplatin should always be administered before fluoropyrimidines, for example 5-fluorouracil.
After the administration of oxaliplatin clean the line with water and then administer 5-fluorouracil.
USE ONLY recommended solvents
Any reconstituted solution that shows evidence of precipitation should not be used and should be destroyed taking into account the legal requirements for the disposal of hazardous waste.
INTERACTION WITH DRUGS
- Due to the incompatibilities with sodium chloride and alkaline drugs (especially 5'fluorouracil), oxaliplatini should not be mixed or administered through the same venous route. (See "Incompatibilities")
- In in vitro studies, no significant shift in oxaliplatin protein binding was observed with the following products: erythromycin, salicylates, granisetron, paclitaxel, sodium valproate.
- In in vivo studies in both animals and man, a synergy was observed when oxaliplatin was combined with 5-fluorouracil. Taxanes can increase the toxicity of oxaliplatin if given prior to it as a sequential infusion.
- Nephrotoxic drugs (aminoglycosides, amphotericin B, iodine contrast agents, methotrexate, pentamidine, acyclovit derivatives, tacrolimus, foscarnet): possible increased nephrotoxicity especially in patients with renal failure.
- Pemetrexed: this is eliminated unchanged via the kidneys, mainly through tubular secretion. Concomitant administration of nephrotoxic drugs such as platinum derivatives could cause a delay in the clearance of pemetrexed. This combination should be used with caution. If concomitant use is necessary, creatinine clearance should be closely monitored.
- Anticoagulants: prothrombin time and INR are prolonged, occasionally associated with bleeding (eg warfarin).
- Fluorouracil: Potential pharmacokinetic interaction in concomitant use. The plasma concentration of fluorouracil is increased by approximately 20%
- Antineoplastic agents: pharmacokinetic interaction with irinotecan or topotecan, unlikely.
- Compounds that affect microsomal liver enzymes: pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 or those that inhibit or induce this isoenzyme are unlikely. However, no studies have been conducted in this regard.
- Bone marrow depressants: the joint use of two or more bone marrow depressants including radiation can cause an additive effect on the bone marrow and gastrointestinal effects.
- INCOMPATIBILITIES: This drug should not be mixed with other drugs in the same infusion bag or infusion line. Oxaliplatin can be co-administered with folinic acid (FA) via a Y line under the conditions described in SPECIAL HANDLING PRECAUTIONS
- DO NOT USE with alkaline solutions or medicines, in particular 5 fluorouracil (5FU), folinic acid (FA) preparations containing trometamol as an excipient and trometamol salts of other medicines. The Alkaline medications or their solutions can adversely affect the stability of oxaliplatin.
- DO NOT RECONSTITUTE or DILUTE oxaliplatin with saline solutions or other solutions containing chloride ions (including calcium, potassium, or sodium chloride).
- DO NOT MIX with other drugs in the same infusion bag or infusion line.
- DO NOT USE injection materials containing aluminum.

PREGNANCY AND FERTILITY:

- There is no information on the safety of the use of oxaliplatin in pregnant women.
- Category D, can cause harm to the fetus when administered to a pregnant woman.
- Oxaliplatin is contraindicated in pregnancy.
- Based on preclinical data, reproductive toxicity was observed in animal studies. Consequently, oxaliplatin is not recommended during pregnancy or in women of childbearing potential not using contraceptive measures. The use of oxaliplatin should only be considered after appropriate information to the patient of the risk to the fetus and with the consent of the patient.
- Appropriate contraceptive measures should be taken during and after cessation of treatment for 4 months in women and 6 months in men.

LACTATION:

- The passage of oxaliplatin into breast milk has not been studied.
- Oxaliplatin is contraindicated during breastfeeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, treatment with oxaliplatin may lead to an increased risk of dizziness, vertigo, nausea and vomiting, and other neurological symptoms that can affect gait and balance and have a slight or moderate influence on the ability to drive or use machines.

Vision disturbances, in particular temporary loss of vision (reversible after stopping treatment), may affect the patient's ability to drive and use machines. Therefore, patients should be warned about the possible consequences of these effects on the ability to drive or use machines.

ADVERSE REACTIONS:

The most frequently observed adverse reactions of oxaliplatin in association with 5-fluorouracil (5-FU) / folinic acid (FA) are gastrointestinal (diarrhea, nausea, vomiting and mucositis), hematological (neutropenia, thrombocytopenia) and neurological (acute peripheral sensory neuropathy and by accumulated doses). In general, these adverse reactions were more frequent and serious in the combination of oxaliplatin and 5-FU / FA, than in the case of 5-FU / FA alone.

The frequencies described in the following table have been extracted from clinical studies carried out in the treatment of metastatic cancer and in adjuvant treatment (which have included 416 and 1,108 patients respectively in the oxaliplatin + 5-FU / FA treatment groups and post-marketing data.

The frequencies in this table are defined by: Very common (> 1/10), common (> 1/100, ≤1 / 10), uncommon (> 1 / 1,000, ≤1 / 100), rare (> 1 / 10,000, ≤1 / 1,000); very rare (≤ 1 / 10,000) including isolated, unknown cases (cannot be estimated from the available data).

Following the table, more detailed information is included.

Adverse reactions by class of organs and systems

Classification MedDRA Organ-system	**Very frequent (≥ 1/10)**	**Frequent (≥1/100, < 1/10)**	**Infrequents (≥1/1.000, <1/100)**	**Rare (≥1/10.000, <1/1.000)**	**Unknown frequencies**
Infections and infestations	Infection	Rhinitis Upper respiratory infection Febrile Neutropenia / Neutropenic Sepsis			
Blood and lymphatic system disorders	Anemia Neutropenia Thrombocytopenia Leukopenia Lymphenia			Immune thrombocytopenia allergic Hemolytic anemia	Pancytopenia autoimmune
Immune system disorders	Allergy/ Allergic reaction+				
Metabolism and nutrition disorders	Anorexy Altered blood glucose Hypokalemia Altered Natremia	Dehydratation	Metabolic acidosis		
Psychiatric disorders		Depression Insomnia	Nervousness		
Nervous system disorders	Peripheral sensory neuropathy Sensory disturbance Dysgeusia Headache	Dizziness Motor neuritis Meningism		Dysarthria	
Eye disorders		Conjunctivitis Vision disturbances		Transient loss of visual acuity Visual field alterations Transient loss of vision, reversible after discontinuation of treatment Optic neuritis	
Ear and labyrinth disorders			Ototoxicity	Deafness	
Vascular disorders	Epitaxis	Hemorrhage Blush Thrombosis venous deep Pulmonary embolism Hypertension			
Respiratory, thoracic and mediastinal disorders	Dyspnoea cough	Hiccup		Interstitial lung disease, sometimes fatal Pulmonary fibrosis	
Gastrointestinal disorders	Sickness Diarrhea Vomiting Stomatitis/ mucositis Abdominal pain Constipation	Dyspepsia Gastroesophageal reflux Gastrointestinal bleeding	Ileus Intestinal obstruction	Colitis, including diarrhea due to *Clostridium difficile*	
Skin and subcutaneous tissue disorders	Skin disorders Alopecia	Skin exfoliation (i.e., hand and foot syndrome) Erythematous rash Rash Hyperhidrosis Nail disorders			Hypersensitivity vasculitis
Musculoskeletal disorders and connective tissue	Back pain	Arthralgia Bone pain			
Renal and urinary disorders		Hematuria Dysuria Altered frequency of urination			
General disorders and administration site conditions	Fatigue Fever++ Asthenia Pain Injection site reaction+++				
Complementary explorations	Increased Lived enzymes Increased serum alkaline phosphatase Increased serum bilirubin Increased serum lactate deshydrigenase Weigth gain (adjuvant treatment)	Increased serum creatinine Weight loss (metastatic cancer treatment)			

Very common allergies / allergic reactions, mainly occurring during infusion, sometimes fatal. Common allergic reactions include skin rash, especially hives, conjunctivitis, and rhinitis. Common anaphylactic or anaphylactoid reactions include bronchospasm, angioedema, hypotension, a sensation of chest pain, and anaphylactic shock. Delayed hypersensitivity has also been reported with oxaliplatin, hours and even days after infusion.

+ Frequent allergic reactions, such as skin rash (especially urticaria), conjunctivitis, rhinitis.

Frequent anaphylactic reactions, such as bronchospasm, angioedema, hypotension, and anaphylactic shock.

++ Very frequent fever, chills (tremors) either of infectious origin (accompanied or not by febrile neutropenia), or isolated fever of immunological origin.

+++ Injection site reactions include local pain, redness, swelling, and thrombosis.

Extravasation can lead to local pain and inflammation that can be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein.

Blood and lymphatic system disorders

Incidence by patient (%) and by grade

Oxaliplatin and 5-FU/AF 85 mg/m2	**Metastatic cancer treatment**			**Adjuvant treatment**		
Each 2 weeks	Every grades	Gr. 3	Gr. 4	Every grades	Gr. 3	Gr. 4
Sickness	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

Post-marketing experience with unknown frequency

Hemolytic uremic syndrome

Immune system disorders

Incidence by patient (%) and by grade

Nervous system disorders

The dose-limiting toxicity of oxaliplatin is neurologic toxicity. This manifests as a sensory peripheral neuropathy characterized by dysesthesias and / or paresthesias of the extremities with or without cramps, often exacerbated by cold. These symptoms appear in 95% of treated patients. The duration of symptoms, which are usually reversible between treatment cycles, increases with the number of cycles.

The appearance of pain and / or functional disorders entail, depending on the duration of the symptoms, a dose adjustment, or even the suspension of treatment.

These functional disorders include difficulty in executing delicate movements and are possibly the consequence of sensory disturbances. The risk of persistent symptoms in the case of a cumulative dose of 850 mg / m^2 (10 cycles) is approximately 10% and 20% in the case of a cumulative dose of 1020 mg / m^2 (m^2 cycles).

In most cases, neurological signs and symptoms improve or completely subside after discontinuation of treatment. When used as adjunctive treatment in colon cancer, 6 months after stopping treatment, 87% of the patients did not show symptoms or they were mild. After up to 3 years of follow-up, about 3% of patients had persistent localized paresthesias of moderate intensity (2.3%) or paresthesias that can interfere with functional activities (0.5%).

Acute neurosensory manifestations have been reported.

They start after several hours of administration and often occur after exposure to cold. They may manifest as transient paraesthesia, dysesthesia, and hypoaesthesia, or as acute pharyngolaryngeal dysesthesia syndrome. This acute syndrome of pharyngolaryngeal dysesthesia, the incidence of which is 1 - 2%, is characterized by subjective sensations of dysphagia and dyspnea / feeling of flushing, without any objective evidence of respiratory distress (absence of cyanosis or hypoxia), or laryngospasm or bronchospasm (absence of stridor or wheezing); Abnormal sensation of the tongue, dysarthria and a feeling of pressure in the chest have also been observed. Although antihistamines and bronchodilators have been administered in these situations, the symptoms are rapidly reversible even in the absence of treatment. The prolongation of the infusion time favors the decrease in the incidence of this syndrome.

Occasionally other symptoms that have been observed include jaw spasms, muscle spasms, involuntary muscle contractions / muscle twitching / myoclonus, abnormal coordination, abnormal gait, ataxia, balance disturbances, throat or chest tightness, pressure, discomfort, pain. In addition, nerve cranial dysfunctions may be associated or also occur as an isolated event such as ptosis, diplopia, aphonia, dysphonia, hoarseness, sometimes described as paralysis of the vocal cords, abnormal sensation of the tongue, or dysarthria, sometimes described as aphasia. neuralgia, trigeminal, facial pain, eye pain, decreased visual acuity, visual field disturbance.

Other neurological symptoms such as dysarthria, loss of deep tendon reflexes, and Lhermitte's sign have been observed during oxaliplatin treatment. Isolated cases of optic neuritis have been reported.

Post-marketing experience of unknown frequency

Convulsions

Gastrointestinal disorders

Incidence by patient (%) and by grade

Oxaliplatin and 5-FU/AF 85 mg/m2	**Metastatic cancer treatment**			**Adjuvant treatment**		
Each 2 weeks	Every grades	Gr. 3	Gr. 4	Every grades	Gr. 3	Gr. 4
Allergic reactions / Allergies	9,1	1	<1	10,3	2,3	0,6

Prophylaxis and / or treatment with strong antiemetics is recommended.

Severe diarrhea / vomiting can lead to dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis, and kidney failure, particularly when oxaliplatin is combined with 5-fluorouracil.

Hepatobiliary disorders

Very rare (<1 / 10,000)

Hepatic sinusoidal obstruction syndrome, also known as veno-occlusive liver disease or pathological manifestations related to liver disorders, including hepatic peliosis, nodular regenerative hyperplasia, perisinusoidal fibrosis. The clinical manifestations can cause portal hypertension and / or elevation of transaminases.

Renal and urinary disorders

Very rare (<1 / 10,000)

Acute tubular necrosis, acute interstitial nephritis, and acute renal failure.

CONTRAINDICATIONS

Oxaliplatin is contraindicated in patients who:

They have a history of known hypersensitivity to oxaliplatin, or to the excipient (lactose).

They are lactating women.

They have myelosuppression before starting the first cycle of treatment, evidenced by neutrophils <2x10^9 / l and / or platelets <100x10^9 / l.

They have peripheral sensory neuropathy with functional impairment before the first drug administration.

They have severe kidney failure (creatinine clearance <30 ml / min).

OVERDOSE:

There is no known antidote. In case of overdose, an exacerbation of adverse effects can be expected. A hematological control should be carried out as well as a symptomatic treatment of other toxic manifestations.

"In the event of an accidental overdose, go to the nearest hospital or contact the toxicology or poisoning centers:

HOSPITAL DE PEDIATRIA RICARDO GUTIERREZ: (011) 4962-6666 / 2247, HOSPITAL A. POSADAS: (011) 4654-6648 and 4658-7777,

or the NATIONAL INTOXICATIONS CENTER: 0-800-333-0160".

STORAGE

Keep the vial in the outer carton. Store between 15 and 30ºC (59° - 86°F) protected from light. Reconstitued: in refrigerator between 2ºC and 8ºC (35.6 46.4 °F) protected from light. Do not freeze.

The opened ampoules must be discard.

This medicine must not be used after expire date.

IF YOU HAVE ANY QUESTIONS, PLEASE CONSULT YOUR DOCTOR

This drug is under an effectiveness and safety monitoring plan.

Reporting of suspected adverse reactions

It is important to report suspected adverse drug reactions. This allows continuous monitoring of the benefit / risk ratio of the medicinal product. Health professionals are invited to report suspected adverse reactions through the ANMAT Pharmacovigilance System to the address: Av. De Mayo 869 Piso 11 CP: AAD 1084BS, by email to: snfvg@anmat.gov.ar, or call ANMAT answer 0800-333-1234"

Contents of container

Original container containing 8 ampoules, 21 ampoules or 48 ampoules for all concentrations

Keep out of the reach of children

Medicine authorized by the Health Ministry. Certificate N°50862

Manufacturer:

Laboratorios IMA S.A.I.C., Palpa No2862, City of Buenos Aires, Argentine Republic

Marketing Authorization Holder:

GP Pharm S.A. Laboratories

Panamá 2121 - Martínez – Pdo. de San Isidro- Pcia de Buenos Aires-CP B1640 DKC. Argentina.

Technical Director: Carlos Donolo, Pharmacist.

ACS20184LB - 01