

Versión Final

Suggested precautions include the following:

* Reconstitute and dilute parenteral medications wearing disposable gloves and surgical masks in a biological restraining office.

* Use of the appropriate technique to avoid contamination of the medication, work area, and people during the transference among containers (including suitable training in this technique of the people involved).

* Careful and appropriate arrangement of needles, syringes, containers, vials, and medications already used.

Some medical centers have written a detailed guide for handling of antineoplastic agents.

DOSAGE AND ADMINISTRATION:

In monochemotherapy or combination therapy, the recommended dose is 130 mg/m², repeated every 3 weeks, when significant phenomena of important toxicity are absent. Oxaliplatin is generally administered by short perfusion from 2 to 6 hours, diluted in a 5% glucose solution with a variable volume from 250 to 500 ml.

Dosage can be modified according to tolerability, mainly neurological tolerability.

Reconstitution of the lyophilized:

The solvents used for the reconstitution of the lyophilized are water for injection or a 5% glucose solution.

Oxaliplatino Servycal 50 mg: Add 10 to 20 ml of solvent to afford an oxaliplatin concentration of 2.5 to 5.0 mg/ ml.

Oxaliplatino Servycal 100 mg: Add 20 to 40 ml of solvent to afford an oxaliplatin concentration of 2.5 to 5.0 mg/ ml.

Administration should not be performed in infusion sets containing aluminum. Dilutions with other medications, alkaline media or sodium chloride solutions in all their possible concentrations should not be performed. (See incompatibilities).

After reconstitution:

In the original vial, the solution may be stored up to 24 hours under refrigeration (2 °C - 8 °C).

Dilution before infusion:

Reconstituted solutions are diluted with 250 ml to 500 ml of a 5% glucose solution, and administered by intravenous infusion. This preparation for infusion can be stored for 6 hours at room temperature below 25 °C or up to 24 hours under refrigeration (2 °C - 8 °C). The appropriate handling and disposal

procedures of the materials should be considered for oxaliplatin and all related objects in contact with it as well. These procedures should fit in with the current recommendations for the treatment of cytotoxic waste.

PRESENTATION:

Carton containing a single dose Oxaliplatino Servycal 50 mg per Vial Lyophilized for injection.

Carton containing a single dose Oxaliplatino Servycal 100 mg per Vial Lyophilized for injection.

Store between 15 °C and 30 °C, protected from light.

In case of overdose, go to the nearest hospital.

KEEP OUT OF REACH OF CHILDREN.

This medicine must be used under medical prescription and supervision, and it must not be repeated without a new prescription.

Medicinal Specialty authorized by Argentine Ministry of Health (ANMAT).

Certificado No. 50.200

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Sale under filed prescription
Made in Argentina

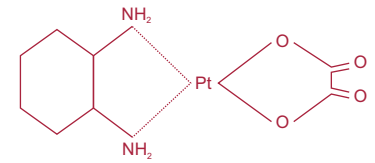
All medications containing Oxaliplatin as an active ingredient, are capable of producing the effects mentioned herein. Oxaliplatin should only be administered by an oncologist.

COMPOSITION:

Each vial of Oxaliplatino Servycal 50 mg contains:
Oxaliplatin 50 mg
Mannitol USP 200 mg

Each vial of Oxaliplatino Servycal 100 mg contains:
Oxaliplatin 100 mg
Mannitol USP 400 mg

- Chemical name : [SP-4-2 (1R-trans)] - (1,2 Cyclohexanediamine-N,N') [ethanedioato (2-) O,O'] platinum.
- Structural formula :



- Molecular formula : C₈H₁₄N₂O₄Pt
- Molecular weight : 397.33
- Chirality : active

THERAPEUTIC ACTION: cytostatic, antineoplastic.

INDICATIONS:

Treatment of metastatic colorectal cancer after previous treatment with fluoropyrimidines in monochemotherapy or combination chemotherapy.

PHARMACOLOGICAL PROPERTIES:

Mechanism of action: Oxaliplatin belongs to a new class of platinum, where the central platinum atom is surrounded by an oxalate group and a 1,2-diaminecyclohexane group in transisomeric position.

Oxaliplatin is a stereoisomer.

Similarly to other platinum derivatives, oxaliplatin acts on the DNA by making alkyl binds which lead to the formation of intrastrand and interstrand crosslinks, and inhibits DNA synthesis and the subsequent DNA replication.

Oxaliplatin binding kinetics on the DNA is fast and takes 15 minutes at the most, while cisplatin's is a two-phase kinetics with a 4 to 8 hour late phase. Cisplatin presence has been proved in human leukocytes 1 hour after treatment administration. In this way, the synthesis by replication and subsequent DNA division is inhibited, as well as secondarily, the RNA and protein synthesis. Oxaliplatin presents antitumoral activity over certain cell lines resistant to cisplatin.

Pharmacokinetic properties:

Following a 2 hour perfusion at a dose of 130 mg/ m², total pallinum peak plasma is 5.1 ± 3.8 ug/ml/h, and the area under the curve (AUC) is 189 ± 45 ug/ml/h.

Distribution and protein binding: At the end of the perfusion procedure, 50% of the platinum has bound to erythrocytes and the other 50 % is in plasma. Considering plasma platinum, 25 % is free and 75 % is bound to proteins. This protein binding index tends to increase and reaches stabilization at around 95% on the fifth day following administration.

Elimination: Elimination is biphasic with a half-life of 40 hours. A maximum of 50 % of the administered dose is excreted in urine in 48 hours (55 % of the dose is excreted in about 6 days).

Fecal excretion is very limited (5 % of the dose after 11 days).

In case of renal impairment, only the clearance of the ultrafiltrating platinum is decreased, without increasing the product toxicity and without being necessary a dosage modification.

The elimination of the erythrocyte-bound platinum is very slow. On day 22, globular platinum reaches 50% of the plasma peak index, while most of the plasma platinum has been eliminated completely. In the course of the subsequent cycles, there is no significant increase in the total plasma platinum and ultracentrifugable platinum indexes; on the contrary, a clear and early accumulation of the globular platinum is observed.

PRECAUTIONS

Pregnancy and lactation:

The information about the safety use of oxaliplatin in pregnant women is not available. Similarly to other cytotoxic agents, oxaliplatin can be toxic to the fetus. Oxaliplatin is contraindicated during pregnancy.

The crossing of oxaliplatin to milk has not been studied. Oxaliplatin is contraindicated during the breastfeeding period.

Special precautions:

Blood cell counts can be decreased by both, disease and treatment. In order to control treatment sufficiently, periodical analyses should be performed.

Symptoms at the peripheral nervous system (aryngopharyngeal spasm and cramps), particularly when having cold drinks after drug administration have been verified. Normally, said symptoms remit without sequelae. Therefore, any abnormal sensation of tingling or pain in toes or throat should be informed to the physician.

Precautions of use:

- Oxaliplatin should not be handled by pregnant women.

- An associated antiemetic treatment can be prescribed in order to avoid nausea and vomiting.

- In case of any doubts, see your doctor.

Drug interactions:

Due to the incompatibility with sodium chloride and other alkaline substances, (5-fluorouracil in particular), oxaliplatin should not be mixed up or administered using the same IV line. (See incompatibilities). No important displacement in oxaliplatin protein binding was observed in vitro with the following products: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

When oxaliplatin was combined in vitro with 5-fluorouracil, both in animals and in human beings, a synergetic effect was observed.

Incompatibilities:

Oxaliplatin should not be administered together with:

- Alkaline medications or alkaline media due to the degradation of oxaliplatin (in particular: an alkaline solution of 5-fluorouracil, tromethamol).

- Chlorides such as sodium chloride in all possible concentrations.

- Alkaline agents such as tromethamol.

- Intravenous administration sets that contain aluminum.

WARNINGS:

Oxaliplatin should be administered under the supervision of a qualified doctor experienced in the use of antineoplastic chemotherapy.

Oxaliplatin neurologic tolerability should be specially supervised, particularly when concomitant medications with potential neurologic toxicity are

administered.

Oxaliplatin digestive toxicity such as nausea and vomiting, accounts for a prophylactic and/or curative antiemetic treatment.

In case of hematologic toxicity (leucocyte counts < 2,000/mm³ or platelet counts < 50,000 mm³), the administration of the following cycle should be put off until recovery is reached.

Precaution of use:

Hematologic analysis before starting treatment as well as before each new therapeutic course should be carried out. Likewise, a neurologic examination, which will be repeated periodically, should be performed before starting treatment

CONTRAINDICATIONS:

Known allergy to platinum derivatives.

Pregnancy.

Lactation.

OVER DOSAGE:

There is no known antidote. In case of overdose, an exacerbation of the adverse effects should be expected.

Hematologic control as well as a symptomatic treatment of other toxic manifestations should be carried out.

ADVERSE EFFECTS:

Hematopoietic system:

Oxaliplatin has low hematologic toxicity. During a monochemotherapy course, the administration of oxaliplatin can lead to the following unwanted effects: anemia, leukopenia, granulocytopenia, thrombocytopenia, sometimes of grade 3 or 4 (severity of grade 4, neutrophil counts < 500/ mm³, platelet counts <25,000/ mm³, hemoglobin < 6.5 g/ 100 ml).

In association with 5-fluorouracil, the hematological toxicity is increased, and is manifested through neutropenia and thrombocytopenia.

Digestive system:

During a monochemotherapy course, oxaliplatin produces nausea, vomiting, and diarrhea. These symptoms can sometimes be severe.

In case of association with 5-fluorouracil, the frequency of said adverse events is increased.

A suitable antiemetic treatment is advised.

Nervous system:

Sometimes, sensitive peripheral neuropathies are observed, characterized by paresthesias of the limbs. Said paresthesias can be accompanied by cramps, dysesthesias of the perioral region and of the upper

aerodigestive pathway, which can resemble clinical manifestations of larynx spasm without anatomical background, spontaneously reversible without sequelae.

These manifestations are caused and even become worse by cold. Paresthesias are generally regressive between treatment cycles, but they can become permanent and lead to functional discomfort after a cumulative dose generally higher than 800 mg/ m² (6 cycles).

Neurotoxicity decreases or disappears in most patients in the following months after treatment withdrawal.

The occurrence of spontaneously reversible paresthesias does not require a dose modification when oxaliplatin is administered later.

Modification of the oxaliplatin dose administered is advised according to the length and severity of the neurologic symptoms observed. In case of persistent paresthesias between two cycles and/or at the onset of a functional disorder, a reduction of 25% of the oxaliplatin dose is recommended (i.e. 100 mg/m²).

If even with a modified dose there would not be any modifications of the symptoms, or symptoms would become worse, interruption of oxaliplatin administration is advised. A new beginning of the oxaliplatin treatment at a complete or reduced dose after a totally or partially symptom regression is possible and it is left to the physician's discretion.

Other effects:

Occasionally, cases of fever, cutaneous rash, and discomfort derived from the injection were observed. During the course of the clinical trials, cases of alopecia, and auditory, renal, hepatic or cardiac toxicity were not observed.

GENERAL INFORMATION ABOUT THE DOSE


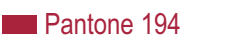

Important:

Do not administer oxaliplatin directly by intravenous line.

Do not mix oxaliplatin with other medications. Each reconstituted solution showing signs of precipitation should be discarded.

Safety factors for handling of this drug.

There exist some limited but growing evidence showing that people involved in the preparation and administration of parenteral antineoplastics agents could be exposed to some risk due to the potential mutagenicity, teratogenicity and/or carcinogenicity of said agents, although the current risk is unknown. The USP guidelines recommend careful handling in the preparation and use of antineoplastic agents.

PRODUCTO: Oxaliplatino Servycal - Ingles - Prospecto			VERSION - 02	
COLORES	ALTERACIONES	Código Actual: 71029-02	 	
 Pantone 194	Emisión inicial: Actualización de textos y nuevo DT.		Aprobado por:	Fecha
	Código anterior:	71029	Desarrollo de Packaging	
	Medida: 220 x 140 mm	 Trazado	Director Técnico	
Fuentes: Frutiger Black Italic – Swis 21 CN BT (resto del texto)			Garantía de Calidad	
Material: Papel Chambriil 56 g/m ² ± 5%.				