

USE IN ELDERLY PEOPLE:

The product should be administered with precaution in elderly people, starting from the lowest doses and with continuous monitoring until deeper experience is acquired.

USE IN HEPATIC AND RENAL DISORDER:

Considering the limited experience available in such cases, that the drug metabolism may be altered in cases of hepatic disorder and that excretion may also be altered, the potential risk-benefit relation of administering the drug to these patients should be considered.

ADVERSE EFFECTS:

The main adverse manifestations occurring due to Paclitaxel administration are: myelosuppression and peripheral neuropathy. Having checked 24 hour and 3 hour infusion programs, neutropenia cases have been less common than in 24 hour infusion regimes. The neutropenia was, in general, quickly reversible and did not become more severe with accumulated exposure. The neurological symptom frequency increased as applications were repeated.

HEMATOLOGICAL: Myelosuppression is the limiting toxicity. Neutropenia is frequent (90%) and sometimes severe. A severe neutropenia lower than 500 cell/mm3 is present in approximately 27% of patients. The previous radiotherapy application does not increase the frequency or severity of neutropenia cases. Neutropenia does not seem to be affected by the treatment duration or accumulated exposures. Infection cases have been reported in around 35%, especially in the urinary tract, upper respiratory tract and sepsis. Thrombocytopenia is less frequent than neutropenia, but it may be severe. Platelet counts below 100,000 cell/ mm³ and 50,000 cell/ mm³ have been reported. The maximum decrease appears between days 8 and 9 after Paclitaxel was administered. Hemorrhage episodes have been reported in 9% of treated patients, who do not need platelet transfusion. Anemia usually occurs in almost all patients, and in some cases, it may be severe (Hd lower than 8g/dl). Anemia incidence and severity has been related to the hemoglobin base-line condition. In these cases, the corresponding treatment must be given. Repeated exposures to Paclitaxel appear to increase anemia's severity.

HYPERSENSITIVITY:

Even under the indicated pre-medication, cases of Paclitaxel hypersensitivity have been reported. These reactions usually appear at the beginning of the treatment and within the first hour of infusion not depending on the dose given. The most frequent manifestations have been dyspnea, flushing, thoracic pain, tachycardia, and hypotension. These effects demand an adequate treatment or the infusion interruption. Most reactions observed were of little significance, as in the case of flushing, rash and hypotension, which do not require the treatment

interruption. Patients who have experienced a severe hypersensitivity reaction must not be exposed to a new treatment with Paclitaxel.

CARDIOVASCULAR:

During Paclitaxel infusion, approximately 24% of patients have been reported to suffer from hypotension, and 4% have been reported to suffer from brachycardia. Brachycardia and hypotension are not usually present during the same course and most of the episodes have been non-symptomatic and have not required treatment. Severe cases of hypotension, venous thrombosis and tachycardia are infrequent, and in the cases reported it was not necessary to discontinue treatment. 13% of patients with a normal electrocardiogram at the beginning of the treatment have been reported to develop an abnormal tracing during the treatment. Such abnormalities have been unspecific such as repolarization, sinus tachycardia and premature heartbeat not clearly related to Paclitaxel administration. So electrocardiogram alterations have had little or no clinical significance.

NEUROLOGIC:

Peripheral neuropathy is dose-dependent in 50% of patients who were non-symptomatic at the base-line and who experienced symptoms during the treatment; in 4% of the patients, the symptoms at recommended doses were severe. Neurological symptoms may appear during the first course and the symptom frequency may be higher as Paclitaxel exposures increase. Pre-existing neuropathies resulting from previous treatments are not a contraindication for the treatment with Paclitaxel. Neurological disorders may rarely include epilepsy and encephalopathy. Sensorial symptoms usually get better or disappear after several months of drug discontinuity.

HEPATIC:

In patients with previous normal hepatic function, the treatment with Paclitaxel causes bilirubin, phosphatase alkaline and Hepatocellular enzymes increases. Fatal cases due to hepatic encephalopathy or hepatic necrosis have rarely been reported.

ARTHRALGIA/MYALGIA:

These effects usually consist in localized pain in legs and arms joints and muscular mass. Approximately 54% of patients treated with Paclitaxel present such symptoms, which are temporary and appear 2 or 3 days after the administration of Paclitaxel. They spontaneously remit a few days later.

REACTIONS IN THE INJECTION AREA:

Paclitaxel endovenous infusion may provoke phlebitis. Extravasations during the infusion causes edema, pain, erythema and induration and, occasionally, may cause cellulitis.

No specific treatment for the extravasation reactions is known yet.

OTHER SECONDARY EFFECTS:

Alopecia affects almost all patients treated with Paclitaxel. Moderate changes have been observed in the skin and nails. At recommended doses, moderate gastrointestinal effects have frequently been observed, such as vomits, diarrhea and mucositis. Some cases of intestinal perforation/obstruction and ischemic colitis have been reported. Although no adverse effect clearly influenced by age has been observed, elderly patients should be treated with precaution; moreover, its safety for pediatric use has not yet been established.

OVERDOSAGE:

No antidote is known for Paclitaxel overdose. Overdose primary manifestations would consist in bone marrow suppression, peripheral neuropathy and mucositis. Overdose treatment consists in the strict treatment prescribed for patients presenting such symptoms.

PRESENTATIONS:

PACLITAXEL SERVYCAL 30. Injectable. PACLITAXEL: Packages containing one vial with concentrate for infusion.
PACLITAXEL SERVYCAL 100. Injectable. PACLITAXEL: Packages containing one vial with concentrate for infusion .
PACLITAXEL SERVYCAL 150. Injectable. PACLITAXEL: Packages containing one vial with concentrate for infusion .
PACLITAXEL SERVYCAL 300. Injectable. PACLITAXEL: Packages containing one vial with concentrate for infusion.

<p>Store between 2 °C and 8 °C (refrigeration temperature) and protec from light. Neither freezing nor refrigeration adversely affects the stability of the product.</p>

Keep out of reach of children.

Medicinal product authorized by Argentine Ministry of Health. (ANMAT). Certificate N°: 50.071

<p>This medicine must be used under medical prescription and supervision, and it must not be repeated without a new prescription.</p>
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Paclitaxel Servycal

Paclitaxel 30, 100, 150 and 300 mg

SOLUTION FOR INJECTION
I.V. INFUSION

SALE UNDER FILED PRESCRIPTION
Made in Argentina

QUALI-QUANTITATIVE COMPOSITION**PACLITAXEL SERVYCAL 30 mg. Injectable.**

Each 30mg.PACLITAXEL SERVYCAL.vial contains:
 PACLITAXEL 30mg, cremophor ELP 2635 mg, dehydrated alcohol quantity enough to 5.0 ml.

PACLITAXEL SERVYCAL 100 mg. Injectable.

Each 100mg.PACLITAXEL SERVYCAL.vial contains:
 PACLITAXEL 100mg, cremophor ELP 8783 mg, dehydrated alcohol quantity enough to 16.7 ml.

PACLITAXEL SERVYCAL 150 mg. Injectable.

Each 150mg.PACLITAXEL SERVYCAL.vial contains:
 PACLITAXEL 150mg, cremophor ELP 13175 mg, dehydrated alcohol quantity enough to 25.0 ml.

PACLITAXEL SERVYCAL 300 mg. Injectable.

Each 300mg.PACLITAXEL SERVYCAL.vial contains:
 PACLITAXEL 300mg, cremophor ELP 26350 mg, dehydrated alcohol quantity enough to 50.0 ml.

TYPE OF AGENT:

Paclitaxel is a natural, anti-tumor product.

INSTRUCTIONS:

PACLITAXEL SERVYCAL is prescribed for the treatment of ovarian or breast metastatic carcinoma after standard therapy has failed.

PHARMACOLOGICAL ACTION: PHARMACODYNAMICS:

Paclitaxel is an anti-microtubule agent. It promotes the assembly of tubuline dimer microtubules, stabilizing them and thus preventing their depolymerisation. The stability achieved inhibits the normal dynamic reorganization of the microtubule network, an essential phenomenon of cell vital functions during interface and mitosis. It also promotes the abnormal formation of microtubule packages and sheaves during the cellular cycle, as well as the generation of multiple grouped formations (asters) of microtubules during mitosis.

PHARMACOKINETICS:

Paclitaxel's pharmacokinetics has been evaluated in cancer patients, in whom its duration varied from 3 to 24 hours. After intravenous administration of Paclitaxel, plasmatic concentration falls in a biphasic way. The quick initial fall represents the distribution in peripheral compartment and the drug metabolization. The subsequent phase is partly due to a slow drug flow from peripheral compartment. Paclitaxel's average life is estimated between 5.3 and 17.4 hours. Body clearance varies between 5.8 and 16.3 l/h/m². The average distribution volume to the balance condition would be between 42 and 162 l/m², which confirms the importance of the drug extra vascular diffusion and tissue fixing. In average, the union with plasma proteins proved to be approximately 89%. The presence of cimetidine, ranitidine, dexamethasone and diphenhydramine does not affect this union. The maximum plasmatic concentrations are proportional to the doses received. No evidence of Paclitaxel accumulation is observed in multiple treatments. Unmodified urinary elimination is between 1.9 and 12.7% of the dose received, which shows an important renal clearance. The existence of an extensive hepatic metabolization is admitted. The main metabolites are the hydroxylated which have been isolated in bile. Hepatic metabolism and biliary clearance may be the main mechanism for Paclitaxel depuration. Paclitaxel's clearance has not been found to be affected by a previous treatment with cimetidine.

DOSAGE -ADMINISTRATION:

The recommended dose is 175mg/mm² administered by intravenous infusion in three hours every three weeks. PACLITAXEL SERVYCAL must not be administered until neutrophiles count is at least 1,500 cells/mm³ and the blood platelet count is 100,000 cells/mm³. Those patients who, in the first administration, have experienced a neutropenia of less than 500 cells/ mm³ or a severe peripheral neuropathy, must receive 20% lower doses in subsequent treatments.

ADMINISTRATION:

PREPARING OF THE PATIENT: All patients who must be treated with PACLITAXEL SERVYCAL must be previously medicated to avoid severe hypersensitivity reactions. Pre-medication may consist in 20 mg dexamethasone orally taken between 12 and 6 hours previous to receiving the drug, 50 mg diphenhydramine intravenously administered 30 to 60 minutes before receiving the drug, and 50 mg ranitidine or 300 mg cimetidine via intravenously 30 to 60 minutes before receiving the drug.

PREPARING FOR THE ADMINISTRATION: PACLITAXEL SERVYCAL concentrated solution contained in each flask shall be diluted before the infusion. The following solutions may be used for dilution: Sodium Chloride Solution at 0.9%. Dextrose Solution at 5% and sodium chloride at 0.9%. Dextrose Solution

at 5% in Ringer solution. In all cases, final Paclitaxel solutions of 0.3 to 1.2 mg/ml (30 mg Paclitaxel in 100 to 25 ml solution respectively) must be obtained. Before being administered, the obtained solutions must be visually checked for particles or color changes. After being prepared, the solution might present a certain turbidity possibly due to the formation of vehicles.

PRECAUTIONS DURING PREPARING: PACLITAXEL SERVYCAL is a cytotoxic anti-blastic product and, as such, must be handled with care. The use of rubber gloves is recommended during all the handling process. If the PACLITAXEL SERVYCAL solution accidentally be in touch with the skin, it must be immediately washed with water and soap. Should the accidental contact be with mucous membranes, they must be washed with abundant water. The contact of PACLITAXEL SERVYCAL with polyvinyl chloride (PVC) equipment must be avoided, in order to prevent ftalate DEHP (di-[2-etilhexil] plasticizer of PVC from releasing and becoming in contact with the patient). To prevent patient contact with said plasticizer, said PACLITAXEL SERVYCAL solution, once diluted, must be kept in glass or polypropylene containers. For infusion administration, the line used must be polyethylene provided with a filter with a lower than 0.22% microns membrane.

STABILITY: The concentrated solution of PACLITAXEL SERVYCAL is stable in its original package (unopened) until its expiration date when stored between 2 °C and 8 °C and protected from light.

Neither freezing nor refrigeration affects the stability of the product.

Precipitation of some crystals of the product may be observed when it is stored at the indicated temperatures giving an opalescence effect in the solution. This condition is reversible with little agitation and upon reaching the product room temperature. If the solution remains opalescent at room temperature, the vial should be discarded. Paclitaxel Servycal should be diluted before its infusion. The prepared solutions for infusion are stable at room temperature (< 25 °C) for no more than 24 hours.

ELDERLY PEOPLE:

PACLITAXEL SERVYCAL must be used with precaution in this group of patients.

PEDIATRIC USE:

Safety and efficiency in children has not been established.

RENAL AND/OR HEPATIC DISORDERS:

In patients suffering from renal or hepatic disorders, PACLITAXEL SERVYCAL must be used with precaution.

CONTRAINDICATIONS:

The treatment with PACLITAXEL SERVYCAL is contraindicated

in those patients with a history of severe Paclitaxel or other compounds formulated with polyoxyethylated castor oil sensitivity. It must not be used in patients with neutropenia lower than 1,500 cells/mm³; in those patients with previous chemotherapy or radiotherapy- induced myelosuppression; or in pregnant or nursing women.

WARNINGS:

PACLITAXEL SERVYCAL must be administered under the supervision of a physician with experience in the use of oncological chemotherapy.

During the treatment, frequent blood tests must be made. PACLITAXEL SERVYCAL must be administered diluted in intravenous infusion. Patients must be pre-treated as indicated in Dosage. Should patients present severe hypersensitivity reaction, the PACLITAXEL SERVYCAL infusion shall be immediately discontinued and Paclitaxel shall not be administered to those patients again. Minor hypersensitivity reactions, such as flush or rash, do not indicate the need to interrupt therapy. The main limiting toxicity of the dose is the suppression of the bone marrow, primary neutropenia. In patients who have presented a severe neutropenia, following doses shall be reduced in a 20%. This dose reduction is also necessary in patients who develop severe neuropathy after the first administration. Severe anomalies in heart conduction have rarely been reported. Should they occur, subsequent administrations shall be performed under continuous heart monitoring. Frequent monitoring of vital signs is recommended, especially during the first hour infusion.

PRECAUTIONS:

During Paclitaxel administration, hypotension and bradycardia have been observed. However, this situation does not usually demand treatment. Frequent monitoring of vital signs is recommended, especially during the first hour of infusion. The occurrence of peripheral neuropathy is frequent, usually not developing serious symptomatology. In such cases, a reduction of 20% in the dose administered in subsequent treatments is recommended. Although there is no evidence of the increase of Paclitaxel toxicity in patients with moderate hepatic dysfunction, there is no data on cases of patients with severe cholestasis. Considering that the liver plays an important role in Paclitaxel metabolism, risk-benefit should be thoroughly considered when Paclitaxel must be administered to patients with severe hepatic damage.

LABORATORY TESTS:

During PACLITAXEL SERVYCAL administration, altered values may be obtained in the following laboratory tests:

- * Alkaline phosphatase results
- * Aspartate-aminotransferase results
- * Bilirubin

* Triglycerides

On a clinical significance basis, the patient previous observation and subsequent monitoring of the following parameters are required before starting the treatment with Injectable PACLITAXEL SERVYCAL:

- * Blood formula counts.
- * Vital signs monitoring.

INTERACTIONS DUE TO THE USE OF OTHER SUBSTANCES:

Research has shown that using scalar doses of Paclitaxel (110-200 mg/m²) and Cisplatin (59 - 75 mg/m²) given as a sequential infusion, myelosuppression was more noticeable when Paclitaxel was administered after Cisplatin than in the inverse manner, i.e., Cisplatin before Paclitaxel. Pharmacokinetic research has shown a Paclitaxel clearance decrease of approximately 33% when it is administered after Cisplatin. Based on in vitro data, it is possible that concomitant administration of Paclitaxel and Ketoconazole might produce certain Paclitaxel metabolism inhibition. Thus, precaution must be taken when administering Paclitaxel to patients receiving Ketoconazol.

CARCINOGENESIS, MUTAGENESIS AND FERTILITY DISORDERS:

Paclitaxel's carcinogenic potential has not been studied. In research done on mammals, Paclitaxel has shown to be mutagenic both in vitro and in vivo. Fertility, implantations and the number of live fetus have shown to diminish in rats. Embryo fetal toxicity was also shown in rabbits.

PREGNANCY:

Paclitaxel may provoke fetus damage if administered during human pregnancy. Fertile women must be warned against becoming pregnant during the treatment. Should the pregnancy occur, the patient must be informed on potential risks.

PREGNANCY AND BIRTH:

Paclitaxel's effect on pregnancy and birth is unknown.

ACTIVE AGENT AND/OR METABOLITE EXCRETION IN MATERNAL MILK:

Whether or not Paclitaxel is excreted through human milk is unknown. Since there is no conclusive proof and considering that the drug may pass to maternal milk, posing a serious risk to the child, it must not be administered during lactation. Thus, patients who must receive the drug must not nurse during the treatment.

PEDIATRIC USE:

Paclitaxel's safety and efficiency in children is unknown..