DELIVERY WORK AND BIRTH: Docetaxel's effect on delivery work and birth is unknown.

ACTIVE AGENT AND/OR METABOLITE EXCRETION IN HUMAN MILK:
Whether or not DOCETAXEL is excreted through human milk is unknown.
Since there is no conclusive proof and considering that the drug may pass to human 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: The safety and efficiency of the use of DOCETAXEL in children have not been established.

USE IN ELDERLY PEOPLE: Appropriate studies regarding the use of DOCETAXEL in elderly people have not been conducted.
Specific disorders in elderly people have not been recorded.
The product should be administered with precaution in elderly people 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.
It should not be prescribed for cases of severe hepatic disorders.

ADVERSE EFFECTS:
The main adverse manifestations occurring due to DOCETAXEL administration are:

HEMATOLOGICAL: Neutropenia which is reversible and non-cumulative is the most frequent adverse reaction associated with DOCETAXEL SERVYCAL.
The average time until nadir is 8 days and the duration of severe neutropenia (lower than 500 cell/mm³) is 7 days.
Studies have been reported where severe neutropenia is present in 75% of the treated patients.
Fever was reported for patients with neutropenia.
Infectious processes, including sepsis and pneumonia, have been reported
Thrombocytopenia is less frequent than neutropenia but it may be severe.
Hemorrhage has been reported.
Anemia usually occurs in almost all patients, and in some cases, it may be severe (HB 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.

HYPERSENSITIVITY: Even under the indicated pre-medication, cases of DOCETAXEL 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, flushing, rash, with or without pruritus, precordial oppression, backache, dyspnea, fever associated with the medication, chills.
Severe reactions were observed - characterized by hypotension, bronchospasm, rash or generalized erythema - a few minutes after the beginning of DOCETAXEL perfusion.
Severe symptoms have been reported in 7% of the patients but only 0.5% required treatment interruption.
All hypersensitivity reactions were solved after perfusion interruption with the appropriate therapy.
Patients who have experienced a severe hypersensitivity reaction must not be exposed to a new treatment with DOCETAXEL.

FLUID RETENTION: Fluid retention has been reported in 47% of the patients

treated. It includes edema and, less frequently, pleural effusion, ascites, pericardial effusion, weight gain.
Fluid retention generally begins in the lower limbs and may become generalized, with a weight gain of 3kg or more.
The appearance of this reaction generally occurs after the fourth cycle of treatment or with a cumulative dose higher or equal to 400 mg/m².
Fluid retention led to treatment interruption in approx 9% of the patients after having received 13 treatment cycles and a cumulative average dose of 1,300 mg/m² .
In patients pre-medicated with corticoids for 4 or 5 days the fluid retention incidence was 33% and of these cases 2% were severe.
Fluid retention was not accompanied by acute episodes of dehydration, oliguria or hypotension and could be reverted slowly after the discontinuation of DOCETAXEL treatment.

CUTANEOUS: Cutaneous reactions have been observed in 64% of the patients treated with DOCETAXEL.
These reactions are characterized by rash, including localized skin eruptions mainly on feet and hands but also on arms, face or thorax. They were sometimes associated with pruritus.
Eruptions generally occurred within a week after DOCETAXEL perfusion and disappeared before the following perfusion and did not represent a physical obstacle.
Severe symptoms such as eruptions followed by desquamation were less frequently observed.
The treatment with DOCETAXEL was seldom interrupted in the presence of these reactions 26% of the patients experienced reactions in the nails.
These reactions were characterized by hypo or hyperpigmentation and less frequently with onycholisis and pain.

NEUROLOGICAL: Mild to moderate neurosensory symptoms were reported in approximately 48% of the cases treated with DOCETAXEL.
These symptoms are characterized by paresthesias, asthenia or pain including burning.
Few cases with severe reactions were reported.
Neuromotor disorders were reported in 14% of the patients, 4% of these reactions were severe.

GASTROINTESTINAL: Episodes of nausea, diarrhea and vomiting which were generally mild to moderate were reported in therapies with DOCETAXEL.
In 5% of the reported cases the gastrointestinal reactions were severe.
Other reactions reported were: anorexia, constipation, estomatitis, esophagitis, changes in the taste.
Intestinal hemorrhages were rarely reported.

CARDIOVASCULAR: Approximately 5% of the patients treated have been reported to suffer form hypotension and out of them 0.5% needed treatment

Less frequent disorders: cardiac insufficiency, paroxysmal atrial tachycardia, atrial flutter, dysrhythmia and hypertension.

HEPATIC: In patients with previous normal hepatic function, the treatment with DOCETAXEL may cause, in approx. 10% of the treated patients the increase of bilirubin, alanine transaminase, alkaline phosphatase and aspartate transaminase.

ARTHRALGIA/MYALGIA: These effects usually consist of localized pain in legs and arm joints and muscular mass. Approximately 10% of patients treated with DOCETAXEL present arthralgia, 22% mialgia.
Symptoms range from mild to moderate.

REACTIONS IN THE INJECTION AREA: The reactions observed in the perfusion area were mild in general.
Reactions included skin sensitivity such as hyper-pigmentation, inflammation,

local erythema, skin dryness or vein inflammation.
DOCETAXEL endovenous perfusion may cause phlebitis.
Extravasation or phlebitis was less frequently observed.
Up to now, no specific treatment is known for extravasation reactions.

OTHER SECONDARY EFFECTS: Alopecia affects almost all patients treated with DOCETAXEL though seldom severely.
Mucositis and asthenia have been reported.

OVERDOSE:
No antidote is known for DOCETAXEL 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.
In the presence of overdose the patient should be under observation in special unit, which includes frequent monitoring of vital signs and general support treatment.
In the rare cases reported of overdose, patients experienced severe neutropenia, mild asthenia, mild cutaneous reactions and mild paresthesia. They recovered without any further complications.

In case of overdosage, go to the nearest Hospital.

PRESENTATIONS:
Injectable DOCETAXEL SERVYCAL 20 mg
DOCETAXEL 20 mg
Packages with a vial of concentrate for perfusion and a vial of diluent

Injectable DOCETAXEL SERVYCAL 80 mg
DOCETAXEL 80 mg
Packages with a vial of concentrate for perfusion and a vial of diluent

KEEP BETWEEN 2 °C AND 8 °C AND, AWAY FROM BRIGHT LIGHT.
KEEP AWAY FROM CHILDREN.
Medicinal Specialty authorized by Argentine Ministry of Health. (ANMAT)
Certificate Nº 50.049

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Revision date: 12/2002

71012-02

Docetaxel Servycal

Docetaxel 20 and 80 mg

INTRAVENOUS CONCENTRATE SOLUTION

MADE IN ARGENTINA
SALE UNDER FILED PRESCRIPTION

THIS MEDICINE MUST BE EXCLUSIVELY USED UNDER MEDICAL PRESCRIPTION AND MUST NOT BE REPEATED WITHOUT A NEW PRESCRIPTION..

COMPOSITION:
INJECTABLE DOCETAXEL SERVYCAL 20mg:

Each vial of concentrate DOCETAXEL SERVYCAL 20 mg contains:	
Anhydrous DOCETAXEL	20.000 mg
Polysorbate 80	500.000 mg
Each vial of diluent DOCETAXEL SERVYCAL 20 mg contains:	
Ethanol 95 %	0.195 ml
Water for injection	1.305 ml

INJECTABLE DOCETAXEL SERVYCAL 80 mg:

Each vial of concentrate DOCETAXEL SERVYCAL 80 mg contains:	
Anhydrous DOCETAXEL	80.000 mg
Polysorbate 80	2000.000 mg
Each vial of diluent DOCETAXEL SERVYCAL 80 mg contains:	
Ethanol 95 %	0.780 ml
Water for injection	5.220 ml

TYPE OF AGENT:
Docetaxel is a semi-synthetic agent that belongs to the taxoid family with antineoplasic activity.

INSTRUCTIONS:
DOCETAXEL SERVYCAL is prescribed for the treatment of advanced or metastatic local breast carcinoma after standard therapy has failed.
Previous therapy should have included antracycline unless contraindicated.
DOCETAXEL SERVYCAL is prescribed for the treatment of advanced o metastatic non small cell lung cancer, for whom platinum based chemotherapy has failed.

PHARMACOLOGICAL ACTION:
PHARMACODYNAMICS:
Docetaxel is an anti-microtubule agent.
It acts through the dissociation of the microtubule network at cellular level which is essential during interface and mitosis.
It promotes the assembly of tubuline in microtubules, stabilizing them and thus preventing their depolymerization.
Docetaxel is fixed to free tubuline diminishing turbuline's critical intra-cellular concentration.
The microtubules stimulated polymerization produces a group of microtubules with abnormal function and microtubule stabilization which results in the mitosis inhibition at cellular level.
The stability achieved inhibits the normal dynamic reorganization of the microtubule network, an essential phenomenon of cell vital functions during interface and mitosis.
Docetaxel fixation to the tubules does not alter the number protofilaments in those microtubules.
In vitro studies showed that docetaxel is cytotoxic for several human and murine tumoral cellular lines as well as for recently removed human tumoral cells.

Doxetaxel is active on several cellular lines over-expressing the p-glycoprotein that codifies the gene that is resistant to multiple drugs.

PHARMACOKINETICS:
Docetaxel pharmacokinetics parameters were assessed in cancer patients after the administration of doses that ranged from 20 to 115 mg/m².
Docetaxel kinetics is dose independent and responds to a three compartment pharmacokinetics model with an average life of 4 minutes, 36 minutes and 11.1 hours for the alpha, beta and gamma phases respectively.
The rapid initial declination represents the distribution in the peripheral compartment.
The subsequent phase is partly due to a slow drug affluence from the peripheral compartment.
Total body clearance average values and distribution volume in the state of equilibrium have been 21 L/h/m² and 113 L respectively.
Pharmacokinetics alterations based on the patient´s age or sex have not been reported for Docetaxel.
With hepatic normal function, elimination is done through defecation in 75% of the cases.
Less than 8% of docetaxel is eliminated unaltered within 48 hours of administration.
Approximately 6% is eliminated through the kidneys.
A 27% reduction in the clearance average in patients with mild to moderate hepatic function insufficiency (Alanine aminotransferase and aspartate aminotransferase values higher or equal to 1.5 times the normal upper limit and alkaline phosphatase higher or equal to 2.5 times the normal upper limit) has been observed.
Docetaxel biotransformation is hepatic.
More than 92% of docetaxel is metabolized within 48 hours in one bigger metabolite and three smaller metabolites.
According to in vitro studies the isoenzymes of cytochrome P450 3A subfamily may be involved in docetaxel metabolism.
Docetaxel bounds to proteins in a ratio higher than 95%.
Dexamethasone presence does not affect this link.

DOSAGE -ADMINISTRATION:
DOSAGE: the recommended dose of DOCETAXEL SERVYCAL is 100 mg/m² administered by intravenous perfusion in one hour every three weeks.
To reduce fluid retention incidence and seventy pre-medication with oral corticoids shall be administered to all patients.
Based on present studies there are no special instructions for its use in elderly patients.

DOSE ADJUSTMENT: PATIENTS WITH NEUTROPENIA, CUTANEOUS REACTIONS OR PERIPHERAL NEUROPATHY
As with many other chemotherapy agents, a careful monitoring of the neutrophiles count is essential for the treatment with DOCETAXEL SERVYCAL .

DOCETAXEL shall not be administered until the neutrophiles count is at least 1,500 cellules/mm³ and the platelet count 100,000 cells/mm³.
The dose shall be reduced from 100 mg/m² to 75 mg/m² to Patients suffering from febrile neutropenia, severe neutropenia (neutrophiles count lower than 500 cells/mm³ over a week), severe or cumulative cutaneous reaction or severe peripheral neuropathy during treatment with DOCETAXEL SERVYCAL.
Should these reactions continue, the dose shall be reduced from 75 mg/m² to 55mg/m². The interruption of treatment is advised if reactions persists.

PATIENTS WITH MILD HEPATIC INSUFFICIENCY
Based on pharmacokinetics studies the DOCETAXEL SERVYCAL recommended dose is
75 mg/m².

ADMINISTRATION:

PREPARING OF THE PATIENT: All patients who need to be treated with DOCETAXEL SERVYCAL must be previously medicated to avoid severe hypersensitivity reactions or fluid retention.
The recommended pre-medication consists in oral pre-medication such as 16 mg. dexamethasone orally taken during 5 days starting one day before each DOCETAXEL SERVYCAL administration.

DRUG PREPARATION BEFORE ADMINISTRATION: The concentrate solution of DOCETAXEL SERVYCAL contained in each flask shall be diluted before perfusion.

PRECAUTIONS DURING PREPARING: DOCETAXEL 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.
Should the DOCETAXEL 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 DOCETAXEL SERVYCAL with polyvinyl chloride (PVC) equipment must be avoided, in order to prevent ftalate DEHP (di- [2-ethiexil] plasticizer of PVC from loosening and becoming in contact with the patient).
To prevent patient contact with said plasticizer, said DOCETAXEL SERVYCAL solution, once diluted, must be kept in glass or polypropylene containers.

DOCETAXEL SERVYCAL PREPARATION BEFORE ADMINISTRATION
1.– Pre-mixture solution preparation:
Take from the refrigerator a sufficient number of vials with the concentrate and diluent DOCETAXEL SERVYCAL.
Let settle for five minutes.
Aseptically add the content of the corresponding diluent vial to each concentrate vial. This procedure shall be carried out using a different needle for each diluent vial.
Agitate manually to help dissolve and let settle for five minutes.
Verify that the obtained solution is clear and limpid (foam formation is normal due to the polysorbate 80 presence).
The pre-mixture solution has a 10 mg DOCETAXEL SERVYCAL concentration/ml.

2.– Perfusion solution preparation
More than one vial of pre-mixture may be needed to obtain the dose required for the patient.
Aseptically transfer with a calibrated syringe the quantity of pre-mixed solution to a vial or bag for perfusion containing 250ml of glucose solution at 5% a or sodium chloride solution at 0.9%.
The solution final concentration shall range between 0.3 and 0.9 mg of DOCETAXEL SERVYCAL per ml.
Should a dose of DOCETAXEL SERVYCAL higher than 240mg be needed, use an infusion, vector higher volume for the concentration not to exceed the 0.9mg DOCETAXEL SERVYCAL ml value.
Manually mix the content of the perfusion vial or bag by rotation and control that the solution is clear and limpid.
The drug administration by perfusion shall be done as soon as possible within one hour period at room temperature submitted at normal light conditions.
All materials used for the reconstitution and administration of DOCETAXEL SERVYCAL.
That are to be disposed of must comply with the procedures in force for said cytostatic waste.

ADMINISTRATION PRECAUTIONS:
DOCETAXEL SERVYCAL shall be intravenously administered.
It is of the utmost importance that the needle or catheter is placed correctly before DOCETAXEL SERVYCAL is injected.
The spreading to the neighboring tissue during administration may cause considerable irritation, local tissue necrosis and / or thrombophlebitis.
Should extravasation occur, the injection must be interrupted immediately

and any remaining portion should be administered through another vein.

STABILITY: The DOCETAXEL SERVYCAL concentrate solution in its original package is stable up to expiry date kept at a temperature of 2 °C to 8 °C protected from light.
The solution, pre-mixed as indicated, is physically and chemically stable for no more than 8 hours kept at room temperature or in the refrigerator and protected from light.

ELDERLY PEOPLE: DOCETAXEL SERVYCAL must be used with precaution in this group of patients although, up to now, there is no clear definition for this type of patients.

PEDIATRIC USE: Safety and efficiency in children has not been established.

RENAL AND/OR HEPATIC DISORDER: In patients suffering from renal or hepatic mild disorders, DOCETAXEL SERVYCAL must be used with precaution.

CONTRAINDICATIONS:
The treatment with DOCETAXEL SERVYCAL is contraindicated in those patients with a history of severe hypersensitivity to DOCETAXEL SERVYCAL or other compounds formulated with polysorbate 80.
It must not be used in patients with neutropenia lower than 1,500 cells/mm³, in those patients with severe hepatic insufficiency; or in pregnant or nursing women.

WARNINGS:
DOCETAXEL SERVYCAL must be administered under the supervision of a physician with experience in the use of chemotherapy.
For the control of complications suitable premises for diagnosis and treatment are needed.
The treatment with DOCETAXEL SERVYCAL is contraindicated in those patients with a history of severe DOCETAXEL SERVYCAL or other compounds formulated with polysorbate 80 sensitivity.
Neutropenia is the most frequent adverse reaction. The average time until nadir is 8 days.
During the treatment, with DOCETAXEL SERVYCAL frequent blood tests must be made.
Patients should not be treated with DOCETAXEL SERVYCAL again until the neutrophiles counts returns to levels over 1,500 cell/mm³.

DOCETAXEL SERVYCAL shall be administered diluted through intravenous perfusion.

Patients must be pre-treated as indicated in Dosage
Should patients present severe hypersensitivity reactions such as hypotension, bronchospasm rash, generalized erythema the DOCETAXEL SERVYCAL perfusion shall be immediately discontinued and DOCETAXEL SERVYCAL shall not be administered to those patients again.
Severe symptoms disappear after the interruption of the perfusion with appropriate therapy.

PRECAUTIONS:
DOCETAXEL SERVYCAL must not be administered until neutrophiles count is at least 1,500 cells/mm³.
To monitor myelotoxicity incidence frequent blood counts are recommended.
Patients must not be administered the drug again until neutrophiles count is at least 1,500 cells/mm³.
In severe neutropenia (lower than 500 cells/mm³ for 7 days or more) while being on DOCETAXEL SERVYCAL treatment a dose reduction is recommended for future therapies.
Hypersensitivity reactions may occur a few minutes after the beginning of perfusion of DOCETAXEL SERVYCAL.
Should only mild reactions such as flushing or dermic reactions occur

treatment does not need to be interrupted.
Should severe reactions such as hypotension, bronchospasm or generalized erythema occur therapy should be interrupted immediately.
Patients who have developed severe hypersensitivity should not be treated with DOCETAXEL SERVYCAL again.
Localized erythema with edema on palms and soles followed by desquamation have been observed.
A dose reduction is recommended for future cycles when severe skin toxicity occurs while undergoing therapy with DOCETAXEL SERVYCAL.
Fluid retention following DOCETAXEL SERVYCAL therapy has been reported
Pre-medicating patients with oral corticoids before therapy is advised.
The development of severe peripheral neurotoxicity is rare and demands a dose reduction.

LABORATORY TESTS:
During DOCETAXEL SERVYCAL administration, altered values may be obtained in the following laboratory tests:
- Higher values for the following results may be obtained:
- Alanine-aminotransferase results.
- Alkaline phosphatase results.
- Aspartate-aminotransferase results.
- Bilirubin concentration.
- Lower results may be obtained for
- Hemoglobin, hematocrit, leukocytes and platelets.

On a clinical significance basis, the patient previous observation and subsequent monitoring of the following parameters are required before starting the treatment with Injectable DOCETAXEL SERVYCAL :
- Blood formula count.
- Hepatic enzimes.
- Vital signs monitoring.

INTERACTIONS DUE TO THE USE OF OTHER SUBSTANCES:
DOCETAXEL SERVYCAL interaction with other drugs has not been studied formally.
In vitro studies show that DOCETAXEL SERVYCAL metabolism may be modified by the concomitant administration of compounds that induce, inhibit or that are metabolized by the cytochrome P450 3A such as: cyclosporine, erythromycin, Ketoconazole, terfenadine, troleandomycin.
Thus, precaution must be taken when administering DOCETAXEL SERVYCAL to patients receiving any of these compounds.

CARCINOGENESIS, MUTAGENESIS AND FERTILITY DISORDERS:
DOCETAXEL SERVYCAL carcinogenic potential has not been studied.
The in vitro Chromosome aberration assay in chinease hamster ovary-KI cell and in the in vivo micronucleous test in mice have showed that DOCETAXEL is mutagenic.
Nevertheless it did not induce mutagenesis in the Ames or in the CHO/HGPRT gene mutation test.
Studies in rats and dogs proved that DOCETAXEL may cause Testicular atrophy or degeneration altering male fertility.

PREGNANCY: No well-controlled and adequate research has been made on pregnant women.
In general, pregnancy is not advisable while undergoing treatment with cytotoxic drugs.
DOCETAXEL may cause fetus damage if administered during human pregnancy.
Teratogenic effects have not been observed with the administration of DOCETAXEL in rats and rabbits, however, some studies proved that DOCETAXEL is embryofetotoxic characterized by intrauterine mortality, reduced fetal weight and delays in ossification.
Fertile women must be warned against becoming pregnant during the treatment.
Should the pregnancy occur, the patient must be informed on potential risks.

PRODUCTO: Docetaxel Servycal - Ingles - Prospecto			**VERSION - 02**
COLORES	ALTERACIONES	Código Actual: 71012-02	SERVYCAL / glenmark
Pantone 194	**Emisión inicial:** Actualización de textos y nuevo DT.		Aprobado por: / Fecha
	Código anterior: 71012		Desarrollo de Packaging
	Medida: 220 x 140 mm	Trazado	Director Técnico
Fuentes: ***Frutiger Black Italic*** – Arial (resto del texto)			Garantía de Calidad
Material: Papel Chambril de 56 g/m² ± 5%.			