

established yet. Doxorubicin has proved to be embryotoxic and teratogenic in rats, and embryotoxic and cause of abortion in rabbits. No well-controlled and adequate research has been made on pregnant women. Should doxorubicin have to be administered during pregnancy, or should the patient believe to be pregnant during the therapy, the patient condition regarding the potential risk to the fetus should be evaluated. Women prone to become pregnant should be advised to take the necessary precautions while they are under treatment with doxorubicin.

**Women during lactation:** Due to the risk of producing adverse reactions in nursing children as a consequence of doxorubicin administration, mothers should be told to discontinue lactation during treatment with doxorubicin.

#### ADVERSE REACTIONS

The limiting toxicities of the doxorubicin dose are myelosuppression and cardiotoxicity. Other reported reactions were the following:

**Cardiotoxicity:** (See WARNING)

**Cutaneous Reactions:** In most cases reversible complete alopecia is observed. Hyperpigmentation of the matrix unguis, wrinkles and dermic folds mainly in children and onycholysis have also been reported in a few of cases. With doxorubicin administration there is also an incidence of cutaneous reactions as a result of previous radiotherapy.

**Gastrointestinal Reactions:** Acute nausea and vomiting were frequently observed and can be severe. These disorders can be reduced with antiemetic therapy. Mucositis (stomatitis and esophagitis) can occur 5 to 10 days after starting administering the medicine. The effect can be severe, which can lead to ulceration, originating severe infections. The dosage regime -the administration of doxorubicin during 3 running days- results in a higher incidence and more severe mucositis. (Ulceration and colon necrosis -mainly the cecum- which leads to hemorrhage or possible fatal infections may occur). This reaction was reported in patients with acute non lymphocytic leukemia treated with a 3-day doxorubicin intake combined with cytarabine. Some cases of anorexia and diarrhea were also reported.

**Vascular reactions:** Phlebosclerosis was reported, especially when very small veins or the same vein were used for the application of the medicine in repeated occasions.

Facial redness can occur if the injection is administered too quickly.

Local: if during the medicine administration a doxorubicin extravasation is produced, severe cellulites and vesication will appear. Furthermore, the formation of erythematous stria along the vein next to the place where the injection was given was reported. (see DOSAGE AND ADMINISTRATION)

**Hematological reactions:** In very few patients treated with doxorubicin together with antineoplastic agents that damage DNA, acute secondary myeloid leukemia with or without preleukemic phase was observed. These cases could have a short latency period (1 to 3 years).

**Hypersensitivity reactions:** Temperature, chills, urticaria were occasionally reported. Anaphylaxis can also occur. A case of an apparent crossing sensitivity with lincmocyin was reported.

**Other adverse reactions:** Very seldom conjunctivitis and lacrimation.

#### OVERDOSE

Overdose with doxorubicin increases the toxic effect of mucositis, leukopenia and thrombocytopenia. The treatment for severe overdose consists of the treatment of the severely myelosuppressed patient's hospitalization, antimicrobial treatment, platelet transfusion and symptomatic treatment of mucositis.

The use of the hemopoietic growth factor can be also considered. The cumulative dose of doxorubicin increases the risk of cardiomyopathy and cardiac congestive problems (see WARNINGS). Treatment consists of the vigorous handling of cardiac congestive disorders with digitalic and diuretic compound remedies and back load reducers such as ACE inhibitors.

#### PACKAGING

One vial of 10 mg and 50 mg.

#### CONSERVATION / PRESERVATION

Keep the vial at temperatures between 15 °C - 30 °C. After the diluent compound is added agitate the vial to dissolve its content thoroughly. The reconstituted solution remains stable at room temperature, protected from the light for 7 days. This solution shall remain stable for 15 days refrigerated (at a temperature of approx. 2 °C - 8 °C). Direct light exposure shall be avoided. Unused remaining content of 10mg and 50mg only dose vials must be completely disposed off. Once the storage term expires the product that has not been used up to that date must be also disposed off.

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

**Keep away from children.**

Medicinal product authorized by the Argentine Ministry of Health, (ANMAT). Certificate No. 49.913

#### SERVYCAL S.A.

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# Doxorubicina Servycal Doxorubicin Hydrochloride 10 mg and 50 mg INJECTABLE LYOPHILIZED

#### SALE UNDER FILED PRESCRIPTION

Made in Argentina

#### QUAL-QUANTITATIVE FORMULA

**DOXORUBICINA SERVYCAL 10 mg**  
Each vial contains:  
Doxorubicin Hydrochloride 10 mg  
Lactose 50 mg

**DOXORUBICINA SERVYCAL 50 mg**  
Each vial contains:  
Doxorubicin Hydrochloride 50 mg  
Lactose 250 mg

#### CATEGORY

Antineoplastic.

#### INSTRUCTIONS AND USE

Successful results were achieved in the application of DOXORUBICINA SERVYCAL to introduce a regression in disseminated neoplastic diseases, such as lymphoblastic leukemia, acute myeloblastic leukemia, Wilms Tumor , neuroblastoma, soft tissue sarcoma and osteosarcoma, breast carcinoma, ovarian carcinoma, transitional bladder carcinoma, thyroid gland carcinoma, gastric carcinoma, "Hodgkin's Disease", malignant lymphoma and lung cancer, particularly the small cell variety.

#### PHARMACOLOGICAL PROPERTIES

##### PHARMACOLOGICAL ACTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from the cultures corresponding to Streptomyces Peuceitius, Var. caesius. Doxorubicin consists of a naphthoquinone nucleus joined to an amino sugar, daunosamin, through a glycosidic link in the ring of "7" atom. In chemical terms, the doxorubicin hydrochloride is: 5, 12 -naphthoquinone, 10-(3-amino-2,3,6-trideoxi-a-L-dexopyranosil) oxil-7,8,9, 10-tetrahydro-6,8,11-trihydro-droxy-8 (hydroxylacetyl)-1 metoxi; hydrochloride (8S-cis) C27 H29 NO 11 HCl. Molecular weight: 579.99

**MECHANISM OF ACTION** :Doxorubicin joins nucleic acids, presumably by a specific intercalation of the planar anthracycline nucleus with the double helix DNA. The anthracycline ring is lipophilic, but the saturated extreme of the ring system contains numerous hydroxyl groups adjacent to the amino sugar. The molecule is anophotic, and contains acid functions in the ring's phenolic groups, and a basic function in the amino sugar group. This drug binds to the cell membranes and to plasmatic proteins.

**DOXORUBICINA SERVYCAL** (Injectable Doxorubicin hydrochloride) is a red-orange lyophilized sterile powder, only for intravenous use. It is available in single dose, 10 mg and 50 mg vials.

Each single dose, 10 mg vial contains 10 mg doxorubicin hydrochloride, 50 mg lactose, in the form of red-orange, lyophilized sterile powder.

Each single dose, 50 mg vial contains 50 mg doxorubicin hydrochloride, 250 mg lactose, in the form of red-orange, lyophilized sterile powder.

#### CLINICAL PHARMACOLGY

Doxorubicin cytotoxic effect on malignant cells and its toxic effects on different organs are believed to be closely related to the nucleotide base intercalation and to cellular membrane lipid bond activities, typical of doxorubicin.

Intercalation is characterized by the inhibition of DNA action and retreat, and ARN polymerases. Apparently, doxorubicin interaction with topoisomerase II, aimed to form complex DNA breakages, is an important mechanism of doxorubicin cytotoxic activity. The doxorubicin-caused cellular membrane bond may affect a variety of cell functions Doxorubicin enzymatic electron reduction by a certain variety of oxidases, reductases and dehydrogenases generates the appearance of extremely reactive species, including hydroxyl OH free radical. The free radical formation has been involved in doxorubicin cardiotoxicity through Cu (II) and Fe (III) reduction at cell level. Research done on animals has shown the existence of activity on a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including a delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy in all essays with dogs and cats. Pharmacokinetic research carried out in patients with different kind of tumors who were receiving a therapy consisting in the application of a single or various agents has proved that doxorubicin adopts a multiphase arrangement after being intravenously injected. The initial, around 5.0 minute distributive average life suggests a fast doxorubicin tissue capture, while the slow tissue elimination process is reflected in a terminal average life of 20 to 48 hours. Distribution volumes at constant condition exceed 23 to 30 l/Kg and show the extensive drug capture in the tissues. Plasmatic clearance is between 8 and 20 ml/min./Kg and prevails due to biliary excretion and metabolism. Around 40% of the dose appears in bile 5 days after the medicine was administered, while only 5% to 12% of the drug and its corresponding metabolites appear in urine during the same period. Doxorubicin bond and its main metabolite (doxorubicinol) with plasmatic protein is around 74 to 78%, being independent from doxorubicin plasmatic concentration, which reaches 2 µM. Enzymatic reduction in position "7", as well as daunosamine sugar breakage produces aglycones that are accompanied by a free radical formation, whose local production may contribute to doxorubicin cardiotoxic activity. From the frequency or formation rate point of view, doxorubicinol (DOX-OL) arrangement in patients is limited. DOX-OL terminal average life is similar to that of doxorubicin.

Compared to that of doxorubicin, DOX-OL relative exposure varies between 0.4 and 0.6. In urine, < 3% of the administered dose was recovered as DOX-OL after 7 days. Regarding doxorubicin and its main metabolite (DOX-OL) pharmacokinetics, medical literature offers no information related to sex differences among the studied patients.

**In four patients:** the existence of a dose-dependent pharmacokinetics was shown in the case of doxorubicin within the 30 to 70 mg/ m<sup>2</sup> dose range. Doxorubicin systemic clearance is significantly reduced in obese women with more than 130% overweight. Moreover, a significant reduction in clearance values was observed, with no changes in the distribution volume, in obese patients as compared with normal patients, with less than 115% overweight. Doxorubicin and doxorubicinol clearance was also reduced in those patients with hepatic function disorders. Doxorubicin was excreted to the milk in a patient in lactation stage, with a milk peak concentration after 24 hours of the beginning of the treatment, of around 4.4 times more than the corresponding plasmatic concentration. Doxorubicin was detected in milk 72 hours after therapy, with a 70 mg/m<sup>2</sup> dose, administered by a 15 minute intravenous infusion, and a cisplatin 100 mg/m<sup>2</sup> dose, administered by a 26 hour intravenous infusion. Doxorubicinol peak concentration in milk, up to 24 hours later, was 0.2 µM, while the AUC curve, up to a 24 hour period, was 15.5 µM/hr. AUC curve for doxorubicin was 9.9 µM/hr. No evidence was found of Doxorubicin getting through the hematoencephalic

barrier.

#### DOSAGE AND ADMINISTRATION

Careful administration of DOXORUBICINA SERVYCAL will reduce the chances of presenting with a perivenous infiltration (see WARNINGS). It may also diminish the chances of local reactions, such as urticaria and erythematous stria formation. Intravenously administered, extravasation may be observed, with or without the pain caused by a subcutaneous injection or a burning feeling, even if the blood returns during the infusion needle aspiration (see DOSAGE). Should any of the extravasation symptoms be observed, the injection or infusion must be immediately concluded and restarted in another vein. If extravasation is suspected, ice shall be applied in the affected area at regular intervals during 15 minutes, four times a day, during three days.

The benefit of local administration of the medicines has not been clearly established. Due to the extravasation reactions' progressive nature, a careful plastic surgery is recommended. Vesicant pain, as well as ulceration and/or persisting pain indicate an exhaustive excision surgery, after a skin graft as chip has been performed. The most usual dosage schedule when a single dose is administered is 60 to 75 mg/m<sup>2</sup>, in a single intravenous injection, administered at 21 day intervals. Patients with low hematimetric counts due to scarce bone marrow reserves, caused by old age, a previous treatment or a neoplastic infiltration, should receive lower doses. DOXORUBICINA SERVYCAL has been concurrently used together with other approved chemotherapy agents. Some evidence shows that the combination of chemotherapeutic agents is much more effective than the administration of a single agent in the treatment of certain diseases. The benefits and risks of this kind of therapy are still to be determined. The most usual dose for this medicine, when administered in combination with another drug therapy, is 40 to 60 mg/m<sup>2</sup> through a 5% sodium chloride or dextrose intravenous infusion, mainly at 21 to 28 day intervals. Doxorubicin dose should be reduced in case of hyperbilirubinemia, as follows.

| PLASMATIC BILIRUBIN CONCENTRATION ( in mg/dL) | DOSE REDUCTION ( in %) |
|---|------------------------|
| 1.2 - 3.0                                     | 50                     |
| 3.1 - 5.0                                     | 75                     |

**Instructions regarding Reconstitution:** DOXORUBICINA SERVYCAL vials containing 10 mg and 50 mg should be reconstituted with 5 ml and 25 ml 0.9% sterile Sodium Chloride, respectively, to obtain a final concentration of 2 mg/ml Doxorubicin Hydrochloride. During reconstitution procedure, an adequate air volume should be maintained in the vial in order to avoid an excessive pressure accumulation. The use of bacteriostatic diluents is not recommended. After the diluent is added, the vial should be shaken to dissolve its content. The reconstituted solution remains stable at room temperature under normal light conditions during 7 days. If refrigerated (at a 2 °C to 8 °C temperature), the solution will remain stable during 15 days. Direct sunlight exposure must be avoided. The unused content in the single dose 10 mg and 50 mg vials must be disposed off. Once the storing period is over, the medicine not used to date must be completely disposed off. DOXORUBICINA SERVYCAL should be slowly administered through a Sodium Chloride intravenous infusion or through Dextrose (at 5%). The application tube should be added to a "Butterfly" needle preferably inserted in a thick vein. If possible, avoid application in veins located on joints or those extremities involved in venous or lymphatic draining. The administration frequency depends on the vein size and the administered dose. However, the dose should be administered in no less than 3 to 5 minutes. The appearance of local erythematous stria along the vein and face flushing indicate that the medicine administration has been too fast. Burning or typical subcutaneous sensations may indicate a perivenous infiltration. In such cases, the infusion should be concluded and restarted in another vein. A perivenous infiltration may occur with no pain. Doxorubicin should not be mixed with heparin or fluorouracil since, according to certain reports, these drugs might be incompatible because a precipitate might be produced. Until compatibility data are obtained, mixing doxorubicin with other drugs is not recommended. Parenteral drug derived products should be visually checked for foreign particles or discoloration before the medicine is administered -whenever the solution and the packaging allow said control.

**Product handling and disposal:** Skin reactions associated with doxorubicin have been reported. In case of an accident affecting the skin, the exposed area must be washed with abundant water and soap, and rinsed. Should the eyes be affected, apply any standard irrigation technique. Gloves and protecting clothes should be worn while administering the medicine. The procedures for a correct handling and disposal of anti cancer drugs should be considered. In this respect, several information standards have already been published. However, there is no general agreement on whether all procedures can be included in a single recommendable standard or principle.

#### WARNING

**1.** A severe tissue necrosis will occur if any extravasation took place during the medicine administration. (See DOSAGE). Doxorubicin should not be administered intramuscularly or subcutaneously.

**2.** The most severe myocardic toxicity due to potentially fatal congestive heart insufficiency can occur, either during therapy or several months after it has finished. The possibility of developing an affected myocardic function based on the existence of a combined number of signs, symptoms and a declination of the left ventricle ejection fraction (LVEF) is estimated in 1% to 2% corresponding to a total cumulative Doxorubicin dose of 300 mg/ m<sup>2</sup>. 3% to 5% when a 400 mg/m<sup>2</sup> dose is administered; 5% to 8% when a 450 mg/m<sup>2</sup> dose is administered, and 8% to 20% when a 500 mg/m<sup>2</sup> dose is administered.

The risk of developing a CHF (Congestive Heart Failure) rapidly increases as Doxorubicin cumulative doses increase, being the dose administered higher than 450 mg/m<sup>2</sup>. Moreover, toxicity may occur when lower cumulative doses are administered to patients who have received a previous mediastinal irradiation, or are being treated with a concurrent cyclophosphamide-based therapy, or have shown a history of heart failure.

**3.** Doses should be reduced in those patients with hepatic function impairment.

**4.** Also, a severe myelosuppression can be observed.

**5.** Doxorubicin must be administered under the supervision of a physician who is competent in the use of chemotherapeutic agents against cancer.

#### CONTRAINDICATIONS

No doxorubicin therapy should be applied to patients with a marked myelosuppression induced by previous treatment with other antitumor agents or radiotherapy. Doxorubicin treatment is contraindicated in the case of patients who have received a previous treatment with cumulative doses of doxorubicin, daunorubicin, idarubicin and/or other anthracycline and anthracenes.

#### WARNINGS

Special attention must be paid to doxorubicin-induced cardiotoxicity. An irreversible myocardic toxicity, manifested in its most severe form, due to different risky and potentially fatal congestive heart failures may occur, either during therapy or several months after therapy has concluded. The possibility of developing a myocardic function based on the existence of a combined number of signs, symptoms and a declination of the left ventricle ejection fraction (LVEF) is estimated in 1% to 2% corresponding to a total cumulative Doxorubicin dose of 300 mg/ m<sup>2</sup>; 3% to 5% when a 400 mg/m<sup>2</sup> dose is administered; 5% to 8% when a 450 mg/m<sup>2</sup> dose is administered, and 8% to 20% when a 500 mg/m<sup>2</sup> dose is administered, through the injection of a bolus every three weeks. The

possibilities of developing a congestive heart failure were reported to be 5 cases over 188 patients (i.e., 3%) when a cumulative 430 mg/m<sup>2</sup> doxorubicin dose is administered, 8/110 patients (7%) with a 575 mg/m<sup>2</sup> dose, and 3/14 patients (21%) with a 728 mg/m<sup>2</sup> dose. The CHF (congestive heart failure) cumulative incidence was 2.2%. A doxorubicin prospective study showed that the cumulative incidence of a congestive heart failure was 5 to 6% when the drug was administered combined with cyclophosphamide, fluorouracil and/or vincristine, to patients suffering from breast cancer or small cell lung cancer. The probability of CHF once several cumulative doxorubicin doses were administered was: 1.5% with a 300 mg/ m<sup>2</sup> dose, 4.9% with a 400 mg/m<sup>2</sup> dose, 7.7% with a 450 mg/m<sup>2</sup> dose and 20.5% with a 500 mg/m<sup>2</sup> dose. Cardiotoxicity may be observed when low doses are administered to patients with a previous mediastinal irradiation, a therapy concurrent with ciclofosfamido or who are elderly. According to other data, a preexisting heart disease has been noticed to be a co-factor in the increase of doxorubicin-caused cardiotoxicity risk. In these cases, heart toxicity may be produced when the administered doses are lower than the recommended cumulative doxorubicin doses. Some research has suggested that the concomitant administration of doxorubicin and calcium channel blocking drugs may also increase the risk of cardiotoxicity caused by doxorubicin. Moreover, the total doxorubicin dose administered to each patient in particular should be considered, as well as the course of the concomitant therapy with other related compounds, such as daunorubicin, idarubicin and mitoxantrone. Several months, or even years, after the doxorubicin therapy has been discontinued, there may be cases of cardiomyopathy and/or congestive heart failure. The risk of suffering from congestive heart failure and other acute manifestations caused by doxorubicin cardiotoxicity may be higher or lower in children than in adults.

Children seem to pose a particular risk regarding the development of a delayed heart toxicity, since doxorubicin-induced cardiomyopathy hinders myocardial growth and the child's maturing. This probably causes a congestive heart failure during the first years of adulthood; as many as 40% of children may present sub-clinical heart disorder, and 5% to 10% of children may develop a congestive heart failure over a long-term follow-up period. This late heart toxicity may be related to the doxorubicin dose. The longer the follow-up period, the greater the frequency by which disorders are detected. The treatment of doxorubicin-induced congestive heart failure includes the use of digitalis, diuretics, after the administration of blood pressure reducers, such as angiotensin converting enzyme (ACE) inhibitors, as well as a low salt diet and complete rest. This kind of treatment may relieve symptoms and improve the patient's functional condition.

**Heart Function Monitoring:** In adult patients, the severe heart toxicity may occur with no history of changes in the Echocardiogram results. Anthracycline-induced cardiomyopathy is usually associated to very typical histopathological changes in an endomyocardic biopsy (EM biopsy) and to a decrease in the left ventricle ejection fraction (LVEF), according to the results obtained from an angiography and a echocardiogram, based on the values of the base line recorded prior to the adopted treatment. However, it was not shown whether the ejection fraction monitoring is useful to predict the moment in which a particular patient is near the maximum tolerable cumulative doxorubicin dose. The heart function should then be carefully monitored during the treatment, in order to minimize the risk of heart toxicity. An assessment of the base line recorded with an Echocardiogram, the LVEF and/or an electrocardiogram are recommended, especially for those patients with increased heart toxicity risk factors (which involves history of heart disease, mediastinal irradiation or a therapy concurrent with cyclophosphamide). In a cumulative doxorubicin dose of, at least, 400 mg/m<sup>2</sup>, subsequent assessments should periodically be made during said therapy. Children have an increased risk condition regarding the possibility of developing heart toxicity after doxorubicin administration and, thus, periodic heart follow-up assessments to monitor this delayed heart toxicity are recommended. In adults, a 10% decrease in LVEF, under the lower limit of a normal or absolute value LVEF, at any level, indicates an impairment of the heart function. In children, the heart function impairment during or after doxorubicin therapy shows a fall recorded in the fractional shortening (FS) by an absolute value of 10 percentile units, or under 20%, and a LVEF decrease under 55%. Usually, if the best results show a doxorubicin-associated heart function impairment, a continued therapy benefit should be thoroughly considered against the risk of producing irreversible heart damage. Acute arrhythmia cases, with risk to the patient's life, have been reported. These disorders occur during doxorubicin administration or within the subsequent two-hour period. There is a high incidence of bone marrow depression, mainly of leukocytes, which demands a careful hematological monitoring. Following the recommended dose schedule, leukopenia is usually transitory, reaching its nadir 10 to 14 days after the treatment, and usually recovering around day 21. In general, during the treatment with the usual doxorubicin doses, a leukocyte counts as low as 1000/mm<sup>3</sup> is expected. Furthermore, erythrocyte and platelet counts should be monitored, since they may also present reduced values. To this effect, hematological toxicity may demand a dose reduction or interruption, or a delay in the delivery of doxorubicin therapy. Persisting severe myelosuppression may result in a super infection or hemorrhage.

Doxorubicin may increase the toxicity of other anti-cancer therapies. In this sense, an exacerbation of cyclophosphamide-induced hemorrhagic cystitis and the 6-mercaptopurine hepatotoxicity increase were reported. Also, an increased radiation-induced toxicity affecting the myocardium, mucosa, skin or liver were reported, as an effect of doxorubicin administration. Since doxorubicin metabolism and excretion are produced mainly through the hepatobile route, the doxorubicin dose toxicity may be increased by the existence of hepatic disorders. Thus, before applying a specific dose, the hepatic function should be evaluated through laboratory conventional tests, such as SGOT, SGPT, alkaline phosphatase and bilirubin (see DOSAGE AND ADMINISTRATION). Cases of colitis manifested by typhilitis (cecal inflammation), bloody fecal matter and severe and even fatal infections have been associated with a combination of doxorubicin daily administered intravenously during three days and cytarabine, administered through a daily continuous infusion during 7 or more days. Being doxorubicin administered intravenously, extravasation can occur, with or without the pain caused by a subcutaneous injection or burning sensation, even when blood returns during the infusion needle aspiration. (See DOSAGE AND ADMINISTRATION). Should any of the typical extravasation signs or symptoms be observed, the injection or infusion must be immediately concluded and restarted in another vein.

#### PRECAUTIONS

Doxorubicin is not an anti-microbial agent.

Information for patients: DOXORUBICINA SERVYCAL typically gives urine a reddish color during the first 1 or 2 days after the medicine has been administered. Patients should be informed of such occurrence during the active therapy period.

**Drug interaction:** According to medical literature, interaction between doxorubicin and the below-mentioned drugs has been observed in humans: cyclosporin, may induce a coma condition or severe seizures; Phenobarbital increases doxorubicin elimination; phenytoin levels can be reduced by the effects of doxorubicin; streptozocin may inhibit hepatic metabolism, while the administration of live vaccines to immunosuppressive patients, including those suffering from cytotoxic chemotherapy, may be risky. Also, medical literature offers information on potential interactions linked to other drugs.

**Laboratory tests:** The initial treatment with doxorubicin demands the patient observation and a periodical blood cell count monitoring, hepatic function tests and a LVEF (See WARNINGS). Like with other cytotoxic drugs, doxorubicin may induce the "tumoral lysis syndrome", and hyperuricemia in patients evidencing fast growing tumors. Adequate pharmacological support measures may prevent or relieve this complication.

**Carcinogenesis, mutagenesis and fertility difficulties:** No formal doxorubicin research on long-term carcinogenicity has been made. Both doxorubicin and related compounds have shown mutagenic and carcinogenic properties when experimental model systems (including bacteria), mammary cells in cultivation and in Sprague-Dawley half-breed rats. The possible adverse effects on male and female fertility, both in experimental humans and animals, were not the object of an appropriate assessment. Testicular atrophy was observed in rats and dogs. The rare occurrence of a variety of chemotherapy-related acute non-lymphocyte leukemia has been reported a couple of years after the treatment with multiple drugs on some neoplasms. Doxorubicin was, on some occasions, among such drugs. The real role played by doxorubicin has not been established yet.

**Pregnancy:** The degree of safety of administering doxorubicin to pregnant women has not been

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| PRODUCTO: Doxorubicina Servycal - Prospecto - Ingles - Frente                                      |  |                         | VERSION - 03.3          |       |
|--|--|-------------------------|-------------------------|-------|
| COLORES  | ALTERACIONES                                     | Código Actual: 71018-03 |                         |       |
|  | <b>Emisión inicial:</b> Actualización de textos. |                         | Aprobado por:           | Fecha |
|  | Código anterior: 71018-02                        |                         | Desarrollo de Packaging |       |
|  | Medida: 220 x 300 ± 1 mm                         |                         | Director Técnico        |       |
|  |  |                         | Garantía de Calidad     |       |
| Fuentes: <b>Frutiger Black Italic</b> – Arial (resto del texto)                                    |  |                         |                         |       |
| <b>Material:</b> Papel Chambril 56 g/m <sup>2</sup> ( Límite interno ± 8% / Límite externo: ± 5%). |  |                         |                         |       |
| <b>Observaciones:</b> Se modifica tipografía y se agrega fecha de revisión del Prospecto.          |  |                         |                         |       |

| PRODUCTO: Doxorubicina Servycal - Prospecto - Ingles - Dorso                                       |  |                         | VERSION - 03.3          |       |
|--|--|-------------------------|-------------------------|-------|
| COLORES  | ALTERACIONES                                     | Código Actual: 71018-03 |                         |       |
|  | <b>Emisión inicial:</b> Actualización de textos. |                         | Aprobado por:           | Fecha |
|  | Código anterior: 71018-02                        |                         | Desarrollo de Packaging |       |
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