Doxotil®

Doxorubicin

Doxorubicin hydrochloride 2mg/ml inj.sol.

1.1 Name of the medicinal product: Doxotil

1.2 Composition: Active substance: Doxorubicin hydrochloride. **Excipients:** Sodium hydrochloride, water for injections.

1.3 Pharmaceutical form: Injectable solution

1.4 Content in active substance: Doxorubicin hydrochloride 2 mg/ml: • 5 ml vial contains 10 mg of Doxorubicin hydrochloride, • 10 ml vial contains 20 mg of Doxorubicin hydrochloride, • 25 ml vial contains 50 mg of Doxorubicin hydrochloride, • 50 ml vial contains 100 mg of Doxorubicin hydrochloride.

1.5 Description - Packaging: • Box that contains 1 glass vial of 5 ml, • Box that contains 1 glass vial of 10 ml, • Box that contains 1 glass vial of 25 ml, • Box that contains 1 glass vial of 50 ml.

1.6 Pharmacotherapeutic group: Cutostatic

1.7 Marketing Authorization Holder: GENEPHARM SA. - 18th km., Marathon Avenue - 153 51 Pallini - Attica - Greece

1.8 Manufacturer: GENEPHARM SA. - 18th km., Marathon Avenue - 153 51 Pallini - Attica- Greece

2. WHAT YOU SHOULD KNOW ABOUT THE DRUG PRESCRIBED TO YOU BY YOUR DOCTOR

2.1 General information: Although it is known that anthracyclines may interfere in a number of biochemical and biological functions in eukaryotic cells, the exact mechanisms of doxorubicin cytotoxic properties have not yet been fully elucidated. Doxorubicin once penetrated into the cell, it mainly binds to chromatin. From experimental indications, it is concluded that doxorubicin forms a DNA-complex by intercalation of its planar rings between nucleotide base pairs. The consequences of this intercalation, include severe alterations in DNA synthesis, in DNA-dependent RNA synthesis and protein synthesis. However, the doxorubicin concentrations required to exert cytotoxic activity through these mechanisms appear to be higher than those achievable at the site of the tumor in the clinical setting. More recent experimental evidence showed that DNA intercalation causes DNA cleavage by topoisomerase II, yielding serious disturbances in the tertiary DNA structure. This effect is observed with drug concentrations that have been found within the clinically therapeutic dose range. It is also known that doxorubicin is involved in oxidation / reduction reactions: a number out of the NADPH-dependent cellular reductases may reduce doxorubicin to semiquinone free radicals, which can in turn react with molecular oxygen for the generation of highly potent cytostatic compounds, such as superoxides, hydroxyl radicals and oxygen peroxide. The formation of free radicals has been implicated for doxorubicin's cardiotoxicity. An additional site of doxorubicin action may be at the cell membrane level: the drug can bind to cell membrane lipids and affect various cellular functions. The cytotoxic action of doxorubicin may be the result of any of the mechanisms already mentioned, or other mechanisms may also exist.

From cell kinetic studies it is concluded that doxorubicin is active throughout the entire cell cycle, including the interphase. Rapidly proliferating tissues, like neoplastic tissues (but also bone marrow, gastrointestinal tract and oral mucosa, hair follicles) are therefore the most sensitive tissues to the cytotoxic actions of doxorubicin.

2.2 Indications: DOXOTIL has caused significant therapeutic response to a number of solid tumors and hematological malignancies, and is commonly used for the regression of the following neoplastic conditions: breast cancinoma, lung cancinoma, transitional cell bladder cancinoma, thyroid cancer, ovarian cancer, bone and soft tissue sarcomas, Hodgkin's disease, non-Hodgkin's lymphomas, neuroblastoma, Wilm's tumor, acute lymphocytic-lymphoblastic leukemia, acute myeloid leukemia.

2.3 Contraindications

In the conditions in which patients should not receive treatment with intravenous Doxotil are included the following:

• persistent myelosuppresion or severe stomatitis from previous treatment with cytotoxic drugs, • presence of generalized infections, • severe hepatic impairment, • severe arrhythmias, myocardial insufficiency, previous heart attact, • previous treatment with anthracyclines up to their maximal cumulative doses, • hypersensitivity to doxorubicin, or other anthracyclines or anthracenediones

The contraindications for intravesical administration include:

• infiltrative tumors that have penetrated the urinary bladder wall, • urinary tract infections, • urinary bladder inflammation, • catheterization problems (e.g. due to bulky intravesical tumors).

2.4 Special precautions and warnings for use

2.4.1 General:

Treatment with DOXOTIL should only be carried out by physicians experienced in chemotherapy and should be performed under strict surveillance, with a number of body functions being carefully monitored.

• *Complete blood count.* It should be performed with special attention to the complete white blood cell count and to the determination of the leukocytic type. Doxorubicin induced myelosuppression, primarily of leukocytes, requires cautious hematologic monitoring, since persistent severe myelosuppression may result in superinfections or hemorrhages. At the recommended dosages and dosing regimens for the treatment of solid tumors, significant leukopenia may occur (1000/mm ^{3} or even lower counts can be expected during treatment with full doses of doxorubicin), however, this type of leukopenia is usually transient and reaches its nadir 10 to 14 days after treatment, while recovery is usually completed before the 21st day. Platelet and red blood cells counts should also be monitored. Hematologic toxicity may require dosage reduction or the discontinuation or delay of treatment with DOXOTIL.

• *Hepatic function evaluation.* Since DOXOTIL is eliminated mainly through the liver and the bile, delayed excretion of the drug can occur in the case of hepatic impairment or disturbed bile outflow and serious secondary adverse events can develop. The commonly used guidelines for dosage reduction in conditions of impaired hepatic function are based on the serum bilirubin levels as follows:

Serum bilirubin	Dosage reduction
1.2 - 3.0 mg/100mL	50%
3.1 - 5.0 mg/100mL	75%

• *Cardiac function.* Cardiotoxicity constitutes a known risk of anthracycline treatment. The most severe and typical form of this toxicity is represented by a delayed cardiomyopathy that is more usually observed with high cumulative doses of the drug and may cause congestive heart failure (CHF). Cardiac function should be evaluated before the beginning of DOXOTIL treatment and should be monitored throughout treatment duration for the minimization of the risk of severe cardiac impairment. Even if endomyocardial biopsy is recognized as the most appropriate diagnostic tool for the detection of anthracycline-induced cardiomyopathy, this invasive examination cannot be performed easily on a routine basis. Regular evaluation of cardiac function during DOXOTIL treatment may include electrocardiogram (ECG) and the evaluation of the left ventricle ejection fraction (LVEF). ECG changes are generally indicative of a transient toxicity, but the reduced height of QRS complex or the prolongation, beyond normal limits, of the mid-systolic interval may be indicative - as well as, a decrease of the LVEF may be - of typical anthracycline-induced cardiomyopathy. The probability of CHF development, that is estimated at approximately 1% to 2%, with a cumulative dose of 300mg/m^2, is increased slowly up to the total cumulative dose of 450 - 550mg/m^2.

Over that level, the risk of CHF development is suddenly increased and it is suggested not to exceed the total cumulative dose of 550mg/m^2. In the presence of other risk factors (e.g. active or latent cardiovascular disease, prior or concurrent radiotherapy to the mediastinal / pericardial area, previous treatment with other anthracyclines / anthracenediones, concurrent use of other cardiotoxic drugs), doxorubicin cardiac toxicity may occur at lower cumulative doses (e.g. total cumulative dose of 400mg/m^2 in patients who received mediastinal radiotherapy). Under these conditions, cardiac function monitoring should be particularly rigid and the benefit-risk ratio for the continuation of treatment with DOXOTIL under circumstances of impaired cardiac function should be carefully evaluated.

• *Extravasation:* Extravasation of DOXOTIL during intravenous injection may cause severe tissue lesions, even necrosis. Venous sclerosis may be caused by an injection into a small vessel or by repeated injections into the same vein. To minimize the risk of drug extravasation and to ensure the rinsing of the vein, it is recommended to administer the drug via an intravenous saline infusion tube with free flow, after ensuring that the needle is well positioned in the vein. Should signs or symptoms of drug extravasation occur during the intravenous administration of DOXOTIL, the drug infusion should be immediately terminated. For the treatment of extravasation, the interventions considered acceptable by the physician / hospital should be immediately utilized. Doxorubicin may reinforce the toxicity of other cytostatic medications. Worsening of cyclophoshamide-induced hemorrhagic cystitis as well as increased hepatotoxicity of 6-mercaptopurine have been reported. Increase of radiation induced toxicity (myocardium, mucous membranes, skin and liver) has been, also, reported.

• Systemic clearance of doxorubicin was found to be reduced in obese patients. Such patients should be carefully monitored, of undergoing treatment with full doses of the drug.

• DOXOTIL may give a red color to the urine for a period of 1-2 days after its administration. Patients should be aware that this event should not be a reason of inquietude.

2.4.2 Pregnancy and Lactation: The safe use of doxorubicin during pregnancy has not been established. Doxorubicin is embyotoxic and teratogenic in rats. It is embryotoxic and can cause abortion in rabbits. Women who can potentially bear children and are going to receive treatment with doxorubicin should be appraised of the potential risk to the fetus and should be advised to avoid pregnancy during the course of treatment.If DOXOTIL must be administered during pregnancy, the potential benefits of the treatment should be carefully weighed against the possible risks for the embryo. Given the mutagenic potential of doxorubicin, DOXOTIL is possible to cause chromosomal damage in human sperms. Therefore men, even women that receive treatment with DOXOTIL should use contraceptive measures. Doxorubicin is excreted in human milk, so women that receive treatment with DOXOTIL should not breast-feed due to the potential of serious harm damage to nursing infants.

2.4.3 Effect on the ability to drive or operate machinery: There have been no reports on special adverse effects regarding the effects of doxorubicin on the ability to drive and/or use machines.

2.4.4 Incompatibilities: Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. DOXOTIL should not be mixed with heparin, cephalothin or dexamethazone sodium phosphate since it has been reported that these drugs are chemically incompatible (formation of a precipitate). The color of DOXOTIL changes from red to blue-purple, during the addition of aminophylline or 5-fluorouracil and this corresponds to an indication of decomposition. DOXOTIL should not be mixed with other cytostatic drugs in the same syringe during the administration of combination chemotherapy regimens.

2.5 Interactions with other drugs or substances: Doxorubicin may reinforce the toxicity of other cytostatic medications. Worsening of cyclophoshamide-induced hemorrhagic cystitis as well as increased hepatotoxicity of 6-mercaptopurine have been reported. Increase of radiation induced toxicity (myocardium, mucous membranes, skin and liver) has been, also, reported.

DOXOTIL is mainly used in combination with other cytotoxic drugs and additive toxicity may occur, especially regarding bone marrow / hematological system and gastrointestinal track. In addition, concomitant use of DOXOTIL with other cytotoxic drugs, which are reported as potentially cardiotoxic (e.g 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers) requires a close monitoring of cardiac function throughout treatment duration.

Doxorubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant medications may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

The combination of DOXOTIL with cytarabine has induced haemorrhage, ulceration and necrosis of colon mucous membrane in patients with acute myeloid leukaemia.

2.6 Dosage: Doxorubicin is a cytotoxic agent that is usually administered to cancer patients via intravenous injection, and when considered necessary, by the intravesical or intra-arterial route.

Intravenous administration: Posology is usually estimated based on the body surface area (mg/m^2). The DOXOTIL dosing regimen that will be administered may vary depending on the therapeutic indication (solid tumors or acute leukemias), as well as on the use of the specific regimen (e.g. as monotherapy or in combination with other cytotoxic agents or as part of a multiple therapeutic approach that includes a combination of surgical procedure and/or radiotherapy and/or hormone therapy).

The intravenous administration of DOXOTIL should be performed with caution. It is recommended that doxorubicin should be administered via the tubing of a freely running intravenous infusion (isotonic saline solution or 5% glucose solution) over a period of 3 to 5 minutes. The aim of this technique is to minimize the risk of thrombosis or perivenous extravasation, which could cause severe cellulitis, vesication and tissue necrosis. A direct injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Treatment of solid tumors: When DOXOTIL is used as monotherapy, the recommended dosage per cycle is 60 - 75mg/m^2 of body surface every three weeks. The drug is usually administered as a single dose per cycle. However, the drug dosage per cycle may also

When DOXOTIL is used in combination with other cytostatic agents with possible overlapping toxicities, the recommended dose per cycle ranges from 30 to 60mg/m ^{2}.

Given the fact that doxorubicin is a myelosuppresive agent, the interval between cycles may need to be increased, or the drug dosage may need to be reduced, in patients whose white blood cell (WBC) counts (particularly neutrophils) are below the range of normal values before any treatment cycle.

The dosage may also need to be reduced in children, the elderly and in pre-treated patients whose marrow reserve may be low. In the presence of impaired hepatic function, it is suggested that dosage of DOXOTIL be reduced .

Treatment of acute leukemia: In the treatment of acute leukemia, bone marrow aplasia constitutes a therapeutic goal, and intensive regimens of combined chemotherapy are implemented. In these conditions, the recommended dose of DOXOTIL is 2.4 mg/kg of body weight (corresponding to approximately 75 - 90 mg/m ^{2}of body surface) and is administered in divided doses on three consecutive days (one cycle). The timing and dosage of the second cycle have to be determined by the condition of both bone marrow and peripheral blood cells. The interval between cycles should, however, be at least 10 days.

Intravesical administration: The intravesically administered DOXOTIL may be used in the treatment of superficial urinary bladder tumors or as a prophylactic measure for the reduction of reversions after transurethral resection. The recommended dose of DOXOTIL for the local intravesical treatment of superficial urinary bladder tumors is from 30 to 50 mg in 25 - 50 mL of saline solution for every infusion, and the most effective concentration is approximately 1.0 mg/ml. After the completion of the infusion, the patient should change position rotatively every 15 minutes. Generally, the solution should remain in the cyst for a period of 1-2 hours. To avoid undue dilution with the urine, the patient must not drink anything for at least twelve hours prior to instillation (this will reduce urine production to approximately 50 mL/hour). The instillations may be repeated at intervals that range from one week to one month, depending on whether the medication is therapeutic or prophylactic. The systemic absorption of doxorubicin after intravesical administration is very low.

Intra-arterial administration: DOXOTIL has also been used via the intra-arterial route in an attempt to provoke significant local activity with reduced general toxicity. Since this technique may be dangerous and cause extensive tissue necrosis, the intra-arterial administration should only be performed by physicians with substantial experience in using this technique.

2.7 Instructions for use/handling: Intravenous administration: DOXOTIL is usually administered intravenously. The solution must be injected in 3-5 minutes by the tubing of a freely flowing intravenous infusion (saline solution), and after it has been checked that the needle has been properly inserted. This technique is used to minimize the risk of thrombosis or perivenous drug extravasation, which would cause severe cellulitis, and tissue necrosis and ensures the rinsing of the vein after drug administration. Injection to small veins and repeated injections to the same vein may cause venous sclerosis.

Protective measures:

The following protective recommendations are given due to the toxic nature of this substance:

- personnel should be trained in good technique for reconstitution and drug handling, - pregnant women should be excluded from working with this drug, - personnel handling DOXOTIL should wear protective clothing: goggles, gowns and disposable gloves and masks, - a designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper, - all items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.

Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution. Medical attention should be sought. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as indicated above.

2.8 Overdosage - Treatment:

Acute overdosage with DOXOTIL causes severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac changes. The treatment of acute overdosage includes hospitalization, intravenous administration of antibiotics, granulocyte and platelet transfusions, as well as management of gastrointestinal and cardiac toxic manifestations. The use of hematopoietic growth factors is considered purposeful. Chronic overdosage when cumulative doses exceed 550mg/m^2, increases the risk of cardiomyopathy and may result in congestive heart failure (CHF). In these cases, the treatment used is the one used for CHF and consists of digitalis formulations, diuretics, peripheral vasodilators and ACE inhibitors.

2.9 Adverse reactions

Myelotoxicity / Hematologic toxicity: Dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) constitutes the principal manifestation of doxorubicin myelotoxicity / hematological toxicity and represents the acute dose-limiting toxicity of this drug. During the course of the most frequently used 3-4 week regimen, the leukocytes / granulocytes nadir values are generally reached 10 to 14 days after the administration of the drug. In patients with normal bone marrow regenerative capacity, the white blood cell counts return to normal by the end of the third week. If severe myelosuppression occurs, bone marrow support (e.g. with primitive peripheral blood cells or growth factors) may be used. Thrombocytopenia and anemia may also occur. Clinical consequences of doxorubicin myelosuppression / hematological toxicity may include fever, infections, sepsis / septicaemia, septic shock, haemorrhage, tissue hypoxia or death. Intravenous antibiotics should be administered when febrile neutropenia is observed.

The occurrence of secondary acute myeloid leukemia, with or without a pro-leukemic phase, has been rarely reported in patients that receive concomitant treatment with doxorubicin in combination with DNA-damaging antineoplastic agents. These leukemias may have a short (1-3 years) latency period.

Cardiotoxicity: Anthracycline induced cardiotoxicity may be manifested by early (acute) or delayed events. Early cardiotoxicity of DOXOTIL consists mainly of sinus tachycardia and/or ECG abnormalities, e.g. non-specific ST-T wave changes, however, tachyarrhythmias, such as premature ventricular contractions, ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have been reported. With the exception of malignant cardiac dysrhythmias, these events are not usually predictive of subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not considered as an indication for discontinuation of DOXOTIL treatment. Delayed cardiotoxicity is represented by characteristic cardiomyopathy, which is clinically manifested by symptoms / indications of ventricular dysfunction / congestive heart failure (such as dyspnea, pulmonary oedema, dependent oedema [e.g. in the ankle], hepatomegaly, ascites, pleural effusion and gallop rhythm). This toxicity appears to be dependent on the cumulative doxorubicin dose and represents the cumulative dose-limiting toxicity of the drug. In a number of trials, the risk of congestive heart failure was evaluated, in the absence of other risk factors, to suddenly increase when the cumulative dose of doxorubicin reaches 550mg/m ^{2}. However, when there is an additional cardiotoxicity risk (e.g. active or latent cardiovascular disease, previous mediastinal radiotherapy, prior / concomitant use of other cardiotoxic drugs), cardiotoxicity may occur at lower cumulative doses. Delayed cardiotoxicity mainly develops during the course of treatment with doxorubicin and up to two to three months later, however late events have also been reported (several months to years after the completion of treatment). Severe cardiac damage may be prevented through regular monitoring throughout the treatment duration. Subacute effects, such as pericarditis and myocarditis have also been reported.

Gastrointestinal toxicity: Mucositis (mainly stomatitis, and less often oesophagitis) may occur in patients that receive doxorubicin treatment. Clinical manifestations of mucositis include pain or burning sensation, erythema, erosions-ulcerations, bleeding and infections. Stomatitis generally occurs almost immediately after drug administration and if severe, it may progress over a few days to mucosal ulcerations. However, most patients recover from this adverse event up to the third week of treatment. Nausea, vomiting and periodically diarrhea and abdominal pain may also occur. Severe vomiting and diarrhea may provoke dehydration. Nausea and vomiting may be prevented or alleviated with the administration of the appropriate antiemetic treatment. The combination of doxorubicin with cytarabine has induced haemorrhage, ulceration and necrosis of colon mucous membrane in patients with acute myeloid leukaemia.

Skin reactions and Hypersensitivity reactions: Alopecia that includes the interruption of beard growth occurs frequently. This adverse event is usually reversible, with regrowth of all hair within 2-3 months after the completion of treatment. Skin flushing, skin and nail hyperpigmentation, photosensitivity and hypersensitivity to irradiated skin (radiation recall reaction) have also been observed. Urticaria and anaphylaxis have been reported in patients that received treatment with doxorubicin. Signs / symptoms of these reactions may vary from skin rush and pruritus to fever, chills and shock. The hand-foot syndrome (Palmar-plantar erythrodysestesia or hand-foot erythema) has also been reported.

Reactions at the Site of Injection: Erythematous streaking along the infused vein does not represent a rare phenomenon and may precede local phlebitis or thrombophlebitis. The risk of phlebitis / thrombophlebitis at the site of injection may be minimized by following the administration procedure recommended. Phlebosclerosis may also occur, especially when doxorubicin is infused repeatedly into a small vein. In case of perivenous drug extravasation, local pain, severe cellulitis and tissue necrosis are observed .

Other Adverse Events: Other adverse events include malaise / fatigue, eye toxicity (conjunctivitis, lacrimation) and hyperuricemia that may also occur as a consequence of the extensive purine catabolism that accompanies the drug-induced rapid cellular necrosis of highly chemo-sensitive tumors (tumor lysis syndrome). Hydration, urine alkalization and allopurinol administration help in the prevention or minimization of the adverse events of hyperuricemia.

Amenorrhea may also occur and treatment with doxorubicin may cause azoospermia in the seminal fluid.

DOXOTIL administration via the intravesical route may cause chemical cystitis and urinary bladder constriction.

2.10 Missed dose: Not applicable

2.11 Self life: It is written on the outer and inner package. In case this date has passed, do not use the product.

2.12 Storage: Store in the refrigerator (2^0- 8^0 C), protected from light.

2.13 Date of last revision of the text: 16/01/2008

3. INFORMATION ON THE RATIONAL USE OF MEDICINES

- This drug was prescribed to you by your doctor only for your specific medical problem. You should not give it to other people or use it for any other disease without first consulting your doctor.
- If any problem with the medicine is experienced during the treatment, tell your doctor or your pharmacist immediately.
- If you have any questions regard-ding the information concerning the medicine you are taking or if you need to be better informed about your medical problem, do not hesitate to request this information from your doctor or your pharmacist.
- In order for the drug that has been prescribed to you to be effective and safe, it must be taken according to the instructions given to you.
- For your safety and good health, it is necessary to read carefully any information concerning the medicine that was administered to you.
- Do not keep medicines in bathroom cabinets, because heat and humidity may spoil the medicine and render it harmful for your health.
- Do not keep medicines that you do not need any more or that have already expired.
- For increased safety, keep all medicines in a safe place away from children.

4. This medicine is given only under physician's prescription.

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