SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADRIMISIN 50 mg Lyophilized Powder for Solution for IV/Intravesical Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains

Active substance:

Doxorubicin hydrochloride	50 mg

Excipients:

Lactose monohydrate	263.15 mg
Methylparaben	5.00 mg

For list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Vial containing lyophilized powder for solution for injection.
Orange-red colored, porous cake or mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADRIMISIN is indicated to produce regression in a variety of neoplastic conditions such as breast, lung, bladder, thyroid gland, ovarian carcinomas, bone sarcoma and soft tissue sarcoma, Hodgkins and non-Hodgkins lymphomas, neuroblastoma, Wilms' tumor, acute lymphoblastic leukemia, acute myeloid leukemia.
ADRIMISIN is indicated for superficial bladder tumors when administered intravesically either after transurethral resection (prophylactic treatment) or therapeutic purposes.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Intravenous administration:
The total doxorubicin dose per cycle may differ according to its use within a specific treatment regimen (e.g. given as a single agent or in combination with other cytotoxic drugs) and according to the indication.

The solution is given via the set of a freely running intravenous infusion, taking not less than 3 minutes and not more than 10 minutes over the injection. This technique minimizes the risk of thrombosis and perivenous extravasation which can lead to severe cellulites, vesication and necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see section 4.4).

Dosage is usually calculated on the basis of body surface area. As a single agent, the recommended standard starting dose of doxorubicin per cycle in adults is 60-75 mg/m^2 of body surface area. The

total starting dose per cycle may be given as a single dose or divided over 3 successive days or in divided doses given on days 1 and 8. Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), each treatment cycle can be repeated every 3 to 4 weeks. If it is used in combination with other antitumor agents having overlapping toxicity, the dosage of doxorubicin may need to be reduced to 30-60 mg/m^2 every 3 weeks.

If dosage is calculated on the basis of body weight, it has been shown that giving doxorubicin as a single dose every three weeks reduces the distressing toxic effect, mucositis. However, there are still some who believe that dividing the dose over three successive days (0.4-0.8 mg/kg or 20-25 mg/m^2 on each day) gives greater effectiveness though at the cost of higher toxicity. If dosage is to be calculated on the basis of body weight, 1.2-2.4 mg/kg should be given as a single dose every three weeks. Administration of doxorubicin in a weekly regimen has been shown to be as effective as the 3-weekly regimen. The recommended dosage is 20 mg/m^2 weekly, although, objective responses have been seen at 16 mg/m^2. Weekly administration leads to a reduction in cardiotoxicity. Dosage may also need to be reduced in children, obese patients and the elderly.

Lower starting doses or longer intervals between cycles may need to be considered for heavily pre-treated patients, or patients with neoplastic bone marrow infiltration (see section 4.4).

The dosage of ADRIMISIN should be reduced in patients with impaired liver function, so as to avoid an increase in global toxicity (see Table 1). It should not be administered in severe hepatic impairment (see section 4.3). Generally speaking, when the bilirubin levels are between 1.2-3 mg/100 ml and the retention of bromosulphtalein (BSF) is 9-15%, it is recommended that half of the normal dose of ADRIMISIN be administered. If the bilirubin levels and the BSF retention are higher than that, a quarter of the normal dose should be administered. Moderate impairment of renal function does not appear to be a sufficient reason for altering the recommended doses, because of the low level of excretion of ADRIMISIN through the kidneys.

Intravesical administration:
The recommended dosage for topical intravesical treatment is 30-50 mg per instillation to be administered at intervals varying from 1 week to 1 month. The frequency of administration and duration of treatment should be determined in each case by the physician depending on whether the treatment is prophylactic or therapeutic.

The limitations related to ADRIMISIN treatment administered intravenously are not applicable for intravesical use as absorption and drug passage into systemic circulation is minimal.

Method of administration
ADRIMISIN is not active if taken orally, and should not be administered either intramusculary or intrathecally. It should be administered by intravenous injection or by topical intravesical administration by means of a catheter. Physiological solution is preferable as a solvent, because it provides an isotonic solution which is known to be better tolerated. ADRIMISIN dissolves completely and rapidly in physiological solution.
Intravenous administration should proceed over 5 to 10 minutes through the set of a freely-running intravenous infusion containing physiological solution, after confirmation that the needle is correctly inserted into the vein. This technique minimizes the risk of thrombosis and perivenous extravasation which could lead to severe cellulites and necrosis. Injection in small veins and repeated injection in the same vein can lead to venous sclerosis. This technique reduces the risk of extravasation of the drug and ensures the washing of the vein after administration.

The recommended concentration is 1 mg/ml for intravesical treatment.

Additional information on special population

Hepatic impairment
Hepatic dysfunction
If hepatic function is impaired, doxorubicin dosage should be reduced according to the following table:

Table 1	
Serum bilirubin levels	**Recommended dose**
1.2-3.0 mg/100 ml	50% Normal dose
>3.0 mg/100 ml	25% Normal dose

Doxorubicin should not be administered to patients with severe hepatic impairment (see section 4.3)

Renal impairment:
No data related to renal impairment are available.

Obese patients:
Dose reduction may be required in obese patients.

Pediatric populations:
Dose reduction may be required in children. No data relating to age-based dose adjustment are available.

Geriatric populations:
Dose reduction may be required in elderly.

4.3 Contraindications

Hypersensitivity to doxorubicin or any other components of the product, other anthracyclines or anthracenediones.

Intravenous (IV) use:
- Persistent myelosuppression
- Severe hepatic impairment
- Severe cardinal insufficiency
- Recent myocardial infarction
- Severe arrhythmias
- Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (see section 4.4).

Intravesical use:
- Urinary infections
- Inflammation of bladder
- Hematuria
- In patients with bladder tumors complicated by urethral stricture which blocks urethral catheterization

4.4 Special warnings and precautions for use

Doxorubicin should only be administered under supervision of a physician who is experienced in cytotoxic treatment.
Patients should recover from acute toxicities of prior cytotoxic treatment (i.e. stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin.
The systemic clearance of doxorubicin reduces in obese patients (>130% of ideal body weight) (see section 4.2).

Cardiac Function
Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e. Acute) Events: Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, and are generally not a consideration for discontinuation of doxorubicin treatment.

Late (i.e. Delayed) Events: Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes *multi-gated* radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2 slowly increases up to the total cumulative dose of 450-550 mg/m^2. Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones and concomitant use of drugs with the ability to suppress

cardiac contractility or cardiotoxic drugs (e.g., trastuzumab). Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.

It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive.

Hematologic Toxicity
Doxorubicin may produce myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopoenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopoenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophile counts return to normal values in most cases by day 21. Thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia or death.

Secondary Leukemia
Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pre-treated with cytotoxic drugs or when doses of the anthracyclines have been escalated. These leukemias can have a 1 to 3 year latency period.

Gastrointestinal
Doxorubicin is emetogenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.
Ulceration and necrosis of the colon may occur leading to bleeding or serious infections which can be fatal in patients with acute non- lymphocytic leukemia treated with polychemotherapy consisting of doxorubicin and cytarabine on three successive days.

Carcinogenesis, Mutagenesis and Impairment of Fertility
Doxorubicin was demonstrated to be genotoxic and mutagenic *in vitro* and *in vivo* tests.
In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin

may cause amenorrhea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.
Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods.

Hepatic functions
The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with doxorubicin. Patients with elevated bilirubin may experience slower clearance of the drug with an increase in overall toxicity. Lower doses are recommended in these patients (see section 4.2). Patients with severe hepatic impairment should not receive doxorubicin (see section 4.3)

Other
Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicities (myocardium, mucosa, skin and liver) have also been reported.
As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of doxorubicin.

Injection site effect
Phlebosclerosis may result from an injection into a small vessel or repeated injections into the same vein.

Extravasation
Extravasation of doxorubicin during intravenous injection may cause local pain, severe tissue lesions (vesication, severe cellulites) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of doxorubicin, the drug infusion should be immediately stopped.

Tumor-Lysis Syndrome
Doxorubicin may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor lysis syndrome.

Vaccinations
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Additional warning and precautions related to other routes of administration
Intravesical route: Administration of doxorubicin by the intravesical route may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort,

necrosis of the bladder wall) and bladder constrictions. Special attention is required for catherization problems (e.g. uretheral obstruction due to massive intravesical tumors).

This product contains 263.15 mg lactose monohydrate as an excipient per vial. However, no warning is required due to route of administration.

This product contains 5.00 mg methylparaben as an excipient per vial. Methylparaben may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

High dose cyclosporine increases the serum levels and myelotoxicity of doxorubicin.

Doxorubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastrointestinal effects (see section 4.4). The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), require monitoring of cardiac function throughout treatment. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

Paclitaxel can cause increased plasma-concentrations of doxorubicin and/or its metabolites when given prior to doxorubicin. However, certain data indicate that a smaller increase is observed when doxorubicin is administered prior to paclitaxel.

In a clinical study, an increase in doxorubicin AUC of 21% was observed when given with sorafenib 400 mg twice daily. The clinical significance of this finding is unknown.

Additional information on special populations:
There is no information related to interaction on special populations available.

4.6 Fertility, pregnancy and lactation

General Principles
Pregnancy category: D

Women of child-bearing potential/Contraception
Women of childbearing potential have to use effective contraception during treatment (see section 4.4).

Pregnancy
Doxorubicin has harmful pharmacological effects on pregnancy/fetus/newborn child.
Due to the embryo-toxic potential of doxorubicin, this drug should not be used during pregnancy unless clearly necessary. If a woman receives doxorubicin during pregnancy or becomes pregnant whilst taking the drug, she should be warned of the potential hazard to the fetus.

Breast-feeding
Doxorubicin is excreted into breast milk. Women should not breastfeed while undergoing treatment with doxorubicin.

Fertility
In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.
Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods.

4.7 Effects on ability to drive and use machines
The effect of doxorubicin on the ability to drive and use machinery has not been stated.

4.8 Undesirable effects
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

The following adverse events have been reported in association with doxorubicin therapy:

Neoplasms Benign and Malignant (including cysts and polyps)
The occurrence of secondary acute myeloid leukemia with or without a preleukemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 year) latency period.
Not known: Acute lymphocytic leukemia and acute myelogenous leukemia.

Blood and lymphatic system disorders
Hematological monitoring should be undertaken regularly in both hematological and non hematological conditions, because of the possibility of bone-marrow depression which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/hematological toxicity may be fever, infections, sepsis/septicemia, septic shock, hemorrhages, tissue hypoxia or death.
Very common: Leucopoenia, neutropenia, anemia and thrombocytopenia

Immunity system disorders
Not known: Anaphylaxis

Metabolism and nutrition disorders
Not known: Anorexia, dehydration and hyperuricemia

Eye disorders
Common: Conjunctivitis
Not known: Keratitis and lacrimation

Cardiac disorders
Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Routine ECG monitoring is recommended. Caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly without premonitory ECG changes.
Common: Congestive heart failure
Not known: Tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reduction

in left ventricular ejection fraction

Vascular disorders
Not known: Phlebitis, thrombophlebitis, thromboembolism, hot flushes and shock.

Gastrointestinal disorders
Very common: Nausea, vomiting and mucositis/stomatitis, diarrhea
Common: Esophagitis, abdominal pain
Not known: Hyperpigmentation of oral mucosa, gastric erosions, gastrointestinal tract bleeding, and colitis.

Hepatobiliary disorders
Very common: Changes in transaminase levels

Skin and subcutaneous tissue disorders
Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally resumes after treatment is stopped.
Very common: Alopecia
Common: Urticaria, skin rashes/itch, skin and nail hyperpigmentation
Not known: Local toxicity, skin changes, photosensitivity, hypersensitivity to irradiated skin ('radiation recall reaction'), acral erythema and plantar-palmar dysaesthesia.

Renal and urinary disorders
Doxorubicin may impart a red color to urine particularly to the first specimen passed after the injection and patients should be advised that is no cause for alarm.

Reproductive system and breast disorders
Not known: Amenorrhea, oligospermia and azoospermia

General disorders and administration site conditions
The risk of thrombophlebitis at the injection site may be minimized by following the procedure for administration recommended above. A stinging or burning sensation at the site of administration signifies a small degree of extravasation and the infusion should be stopped and re-started in another vein.
Very common: Fever, asthenia and chills
Not known: Malaise

Investigations
Very common: ECG abnormalities

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Centre (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose
Single doses of 250 mg and 500 mg of doxorubicin have proved fatal. Such doses may cause acute

myocardial degeneration within 24 hours and severe myelosupression (mainly leucopenia and thromobocytopenia), the effects of which are greatest between 10 and 15 days after administration. Treatment should aim to support the patient during this period and should utilize such measures as blood transfusions and protective isolation.
Acute overdose with doxorubicin will result in gastrointestinal toxic effects (mainly mucositis). This generally appears early after drug administration, but most patients recover from this within three weeks.
Delayed cardiac failure may occur up to 6 months after the overdose. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents
ATC code: L01DB01

Doxorubicin is an anti-tumor agent. Tumor cells are probably killed through drug-induced alterations of nucleic acid synthesis although the exact mechanism of action has not yet been clearly elucidated.

Proposed mechanism of action includes:
DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to certain constituents of cell membranes (particularly to the membrane lipids, spectrin and cardiolipin). Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.

5.2 Pharmacokinetic properties

General properties

Absorption:
Not applicable.

Distribution:
After IV administration, the plasma disappearance curve of doxorubicin is triphasic with half-lives of 12 minutes, 3.3 hours and 30 hours. The relatively long terminal elimination half-life reflects doxorubicin's distribution into a deep tissue compartment. Only about 33 to 50% of fluorescent or tritiated drug (or degradation products), respectively, can be accounted for in urine, bile and feces for up to 5 days after IV administration. The remainder of the doxorubicin and degradation products appear to be retained for long periods of time in tissues.

Biotransformation:
In cancer patients, doxorubicin is reduced to adriamycinol, which is an active cytotoxic agent. This reduction appears to be catalyzed by cytoplasmic NADPH (nicotinamide adenine dinucleotide phosphate)-dependent aldo-keto reductases that are found in all tissues and play an important role in determining the overall pharmacokinetics of doxorubicin.

Elimination:
Microsomal glycosidases present in most tissues split doxorubicin and adriamycinol into inactive aglycones. The aglycones may then undergo 0-demethylation, followed by conjugation to sulphate or glucuronide esters, and excretion in the bile.

5.3 Preclinical safety data
Doxorubicin was demonstrated to be genotoxic and mutagenic *in vitro* and *in vivo* tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Powder:
Lactose monohydrate
Methylparaben
Diluent:
Water for injections

6.2 Incompatibilities
Doxorubicin should not be mixed with heparin as a precipitate may form. It is not recommended that doxorubicin be mixed with other drugs. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.
Doxorubicin should not be mixed with fluorouracil (eg, in the same IV infusion bag or at the Y-site of an IV infusion line) since it has been reported that these drugs are incompatible to the extent that a precipitate might form. If concomitant therapy with doxorubicin and fluorouracil is required, it is recommended that the IV line be flushed between the administration of these drugs.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at room temperature below 25 °C. Protect from light.
Reconstituted product can be stored at room temperature (at 25°C) for 24 hours and in a refrigerator (at 2-8°C) for 48 hours.

6.5 Nature and contents of container
50 ml glass vials- with rubber stopper and aluminum flip-off cap and an ampoule containing 25 ml of water for injections.
Each carton box contains 1 vial and 1 diluent ampoule.

6.6 Special precautions for disposal and other handling of waste of human medicinal product
Any unused product or waste material should be disposed of in accordance with local requirements.

The following protective recommendations are given due to the toxic nature of this substance:
- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns, 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 and absorbent paper.

- All items for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution (preferably soaking the solution first and then water).
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not graze the skin by using a scrub brush.
- In case of contact with eye(s), hold back the eyelid(s) and flush the affected eyes with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

7. MARKETING AUTHORIZATION HOLDER

Saba İlaç San. ve Tic. A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1 Kat:1
34303 Küçükçekmece – ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER(S)

228/43

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization: 31.12.2010
Date of renewal:

10. DATE OF REVISION OF THE TEXT

19.04.2017