

Prescribing information

ADRIBLASTINA PFS Vials

WARNING

1. Severe local tissue necrosis will occur if there is extravasation during administration (see Dosage and administration). Doxorubicin must not be given by the intramuscular, subcutaneous or intrathecal route.
2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure (CHF) may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m² of doxorubicin, 3 to 5% at a dose of 400 mg/m², 5 to 8% at 450 mg/m² and 6 to 20% at 500 mg/m². The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 450 mg/m². This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy or with pre-existing heart disease.
3. Dosage should be reduced in patients with impaired hepatic function.
4. Severe myelosuppression may occur.
5. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*.

Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine.

Chemically, doxorubicin hydrochloride is:

5,12-naphthacenedione,10-[3-amino-2,3,6-tri-deoxy- α -L-xyo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-, hydrochloride (8S-cis).

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins.

Adriblastina PFS (Doxorubicin Hydrochloride Injection, USP) is a sterile parenteral, isotonic solution for intravenous use only, containing no preservative, available in 5 mL (10 mg) and 25 mL (50 mg) vials.

Each mL contains doxorubicin HCl 2 mg. USP and the following inactive ingredients: sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target pH of 3.0.

Clinical pharmacology

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA

polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytotoxic activity. Doxorubicin cellular membrane binding may effect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical OH \cdot . Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level.

Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphasic disposition after intravenous injection. The initial distributive half-life of approximately 5.0 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin up to 2 μ M. Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol (DOX-OL) in patients is formation rate limited. The terminal half-life of DOX-OL is similar to doxorubicin. The relative exposure of DOX-OL, compared to doxorubicin ranges between 0.4 to 0.6. In urine, <3% of the dose was recovered as DOX-OL over 7 days. The literature contains no information regarding gender related differences in the pharmacokinetics of doxorubicin and doxorubicinol.

In four patients, dose-independent pharmacokinetics have been shown for doxorubicin in the dose range of 30 to 70 mg/m². Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight. The clearance of doxorubicin and doxorubicinol was also reduced in patients with impaired hepatic function. Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.4-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m² of doxorubicin given as a 15 minute intravenous infusion and 100 mg/m² of cisplatin as a 26 hour intravenous infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.2 μ M and AUC up to 24 hours was 16.5 μ M-hr while the AUC for doxorubicin was 9.9 μ M-hr. Doxorubicin does not cross the blood brain barrier.

Indications

Adriblastina PFS has been used successfully to produce regression in a variety of neoplastic conditions, such as carcinoma of the breast, lung, bladder, thyroid, and also ovarian carcinomas, bone and soft-tissue sarcomas, Hodgkin's and non-Hodgkin's lymphomas, neuroblastomas, Wilms' tumor, acute lymphoblastic leukemia and acute myeloblastic leukemia.

Contraindications

Doxorubicin therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antitumor agents or by radiotherapy. Doxorubicin treatment is

contraindicated in patients who received previous treatment with complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthraenes.

Warnings

Special attention must be given to the cardiotoxicity induced by doxorubicin. Irreversible myocardial toxicity, manifested in its most severe form by life threatening and potentially fatal congestive heart failure, may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function, based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m² of doxorubicin, 3 to 5% at a dose of 400 mg/m², 5 to 8% at a dose of 450 mg/m² and 6 to 20% at a dose of 500 mg/m² given on a schedule of a bolus injection once every 3 weeks (data on file at Pharmacia). In a retrospective review by Von Hoff *et al*, the probability of developing congestive heart failure was reported to be 5/168 (3%) at a cumulative dose of 430 mg/m² of doxorubicin, 8/110 (7%) at 575 mg/m² and 3/14 (21%) at 728 mg/m². The cumulative incidence of CHF was 2.2%. In a prospective study of doxorubicin in combination with cyclophosphamide, fluorouracil and/or vincristine in patients with breast cancer or small cell lung cancer, the cumulative incidence of congestive heart failure was 5 to 6%. The probability of CHF at various cumulative doses of doxorubicin was 1.5% at 300 mg/m², 4.9% at 400 mg/m², 7.7% at 450 mg/m² and 20.5% at 500 mg/m².

Cardiotoxicity may occur at lower doses in patients with prior mediastinal irradiation, concurrent cyclophosphamide therapy and advanced age. Data also suggest that pre-existing heart disease is a co-factor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may occur at doses lower than the respective recommended cumulative dose of doxorubicin. Studies have suggested that concomitant administration of doxorubicin and calcium channel entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin, idarubicin and mitoxantrone. Cardiomyopathy and/or congestive heart failure may be encountered several months or years after discontinuation of doxorubicin therapy.

The risk of congestive heart failure and other acute manifestations of doxorubicin cardiotoxicity in children may be as much or lower than in adults. Children appear to be at particular risk for developing delayed cardiac toxicity in that doxorubicin induced cardiomyopathy impairs myocardial growth as children mature, subsequently leading to possible development of congestive heart failure during early adulthood. As many as 40% of children may have subclinical cardiac dysfunction and 5 to 10% of children may develop congestive heart failure on long-term follow-up. This late cardiac toxicity may be related to the dose of doxorubicin. The longer the length of follow-up the greater the increase in the detection rate.

Treatment of doxorubicin induced congestive heart failure includes the use of digitalis, diuretics, after load reducers such as angiotensin I converting enzyme (ACE) inhibitors, low salt diet, and bed rest. Such intervention may relieve symptoms and improve the functional status of the patient.

Monitoring cardiac function
In adult patients severe cardiac toxicity may occur precipitously without antecedent ECG changes.

Cardiomyopathy induced by anthracyclines is usually associated with very characteristic histopathologic changes on an endomyocardial biopsy (EM biopsy), and a decrease of left ventricular ejection fraction (LVEF), as measured by multi-gated radionuclide angiography (MUGA scans) and/or echocardiogram (ECHO), from pretreatment baseline values. However, it has not been demonstrated that monitoring of the ejection fraction will predict when individual patients are approaching their maximally tolerated cumulative dose of doxorubicin. Cardiac function should be carefully monitored during treatment to minimize the risk of cardiac toxicity. A baseline cardiac evaluation with an ECG, LVEF, and/or an echocardiogram (ECHO) is

recommended especially in patients with risk factors for increased cardiac toxicity (pre-existing heart disease, mediastinal irradiation, or concurrent cyclophosphamide therapy). Subsequent evaluations should be obtained at a cumulative dose of doxorubicin of at least 400 mg/m² and periodically thereafter during the course of therapy.

Children are at increased risk for developing delayed cardiotoxicity following doxorubicin administration and therefore a follow-up cardiac evaluation is recommended periodically to monitor for this delayed cardiotoxicity. 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.

In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function. In children, deterioration in cardiac function during or after the completion of therapy with doxorubicin is indicated by a drop in fractional shortening (FS) by an absolute value of \geq 10 percentile units or below 29%, and a decline in LVEF of 10 percentile units or an LVEF below 55%. In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage.

Acute life-threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematologic monitoring. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir 10 to 14 days after treatment with recovery usually occurring by the 21st day. White blood counts as low as 1000/mm³ are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or hemorrhage. Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported. Radiation induced toxicity to the myocardium, mucosae, skin and liver have been reported to be increased by the administration of doxorubicin.

Secondary leukemia

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

Since metabolism and excretion of doxorubicin occurs predominantly by the hepatobiliary route, toxicity to recommended doses of doxorubicin can be enhanced by hepatic impairment; therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin (see Dosage and administration).

Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin given by i.v. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle (see Dosage and administration). If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein.

Pregnancy Category D – Safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no adequate and well-controlled studies in pregnant women. If doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

Precautions

General

Doxorubicin is not an antimicrobial agent.

Information for patients

Adriablastina PFS imparts a red coloration to the urine for 1 to 2 days after administration, and patients should be advised to expect this during active therapy.

Carcinogenesis, mutagenesis, impairment of fertility

Formal long-term carcinogenicity studies have not been conducted with doxorubicin. Doxorubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models (including bacterial systems, mammalian cells in culture, and female Sprague-Dawley rats).

The possible adverse effect on fertility in males and females in humans or experiments on animals have not been adequately evaluated. Testicular atrophy was observed in rats and dogs. A variant of chemotherapy-related acute non-lymphocytic leukemia has been reported to occur infrequently a few years after multiple drug treatment of some neoplasms, which sometimes included doxorubicin. The exact role of doxorubicin has not been elucidated.

Nursing mothers

Because of the potential for serious adverse reactions in nursing infants from doxorubicin, mothers should be advised to discontinue nursing during doxorubicin therapy.

Drug interactions

Literature contain the following drug interactions with doxorubicin in humans: cyclosporine (Sandimmune) may induce coma and/or seizures, phenobarbital increases the elimination of doxorubicin, phenytoin levels may be decreased by doxorubicin, streptozocin (Zanosar) may inhibit the hepatic metabolism, and administration of live vaccines to immunosuppressed patients, including those undergoing cytotoxic chemotherapy, may be hazardous. Information on other potential drug interactions may be found in the literature.

Laboratory tests

Initial treatment with doxorubicin requires observation of the patient and periodic monitoring of complete blood counts, hepatic function tests, and radionuclide left ventricular ejection fraction (see Warnings section).

Like other cytotoxic drugs, doxorubicin may induce "tumor lysis syndrome" and hyperuricemia in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Adverse reactions

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity. Other reactions reported are:

Infections and infestations: infection, sepsis/septicemia

Neoplasms benign and malignant: acute lymphocytic leukemia, acute myelogenous leukemia

Blood and lymphatic system disorders: leukopenia, neutropenia, anemia, thrombocytopenia

Immune system disorders: anaphylaxis

Metabolism and nutrition disorders: anorexia, dehydration, hyperuricemia

Eye disorders: conjunctivitis/keratitis, lacrimation

Cardiac disorders: cardiotoxicity (see Warnings), sinus tachycardia, tachyarrhythmias, atrioventricular and bundle branch block, congestive heart failure

Vascular disorders: hot flashes, phlebitis, thrombophlebitis, phlebosclerosis, thromboembolism, shock

Gastrointestinal disorders: nausea/vomiting, mucositis/stomatitis, hyperpigmentation of oral mucosa, esophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, ulceration and necrosis of colon, diarrhea, colitis

Skin and subcutaneous tissue disorders: alopecia, local toxicity, rash/itch, skin changes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin ("radiation recall reaction"), urticaria, acral erythema, palmar plantar erythrodysesthesia.

Renal and urinary disorders: red coloration of urine for 1 to 2 days after administration

Reproductive system and breast disorders: amenorrhea, oligospermia, azoospermia

General disorders and administration site conditions: malaise/asthenia, fever, chills. A case of apparent cross sensitivity to lincosycin has been reported.

Investigations: ECG abnormalities, asymptomatic reductions in left ventricular ejection fraction, changes in transaminase levels

Local: severe cellulitis, vesication and tissue necrosis will occur if extravasation of doxorubicin occurs during administration. Erythematous streaking along the vein proximal to the site of injection had been reported (see Dosage and administration).

Overdosage

Acute overdosage with doxorubicin enhances the toxic effect of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antimicrobials, platelet transfusions and symptomatic treatment of mucositis. Use of hemopoietic growth factors (G-CSF, GM-CSF) may be considered. Cumulative dosage with doxorubicin increases the risk of cardiomyopathy and resultant congestive heart failure (see Warnings section). Treatment consists of vigorous management of congestive heart failure with digitalis preparations, diuretics, and after-load reducers such as ACE inhibitors.

Dosage and administration

Adriablastina PFS is not active orally, and must not be administered intramuscularly or intrathecally. Adriablastina PFS should be administered solely by intravenous injection or – in the case of local-regional treatment of tumors – by slow intra-arterial infusion.

Care in the administration of Adriablastina PFS will reduce the chance of perivenous infiltration (see Warnings). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. x 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.⁽¹⁾

Intravenous route: When Adriablastina PFS is used as a single antitumor agent the recommended dose in adults is 60-75 mg/m² of body surface area by intravenous injection every three weeks dependent on bone-marrow reserves. The lower dose (60 mg/m²) is recommended for patients

with inadequate marrow reserves as a result of old age, previous therapy or neoplastic marrow infiltration. The above dose can be given as a single injection or subdivided over 2-3 consecutive days. An alternative dosage of 30 mg/m²/day i.v. for three consecutive days has been suggested specifically for pediatric use: the course should be repeated every 4 weeks.

The cumulative dose of Adriablastina PFS by the intravenous route, irrespective of the dosage schedule, should not exceed 550 mg/m² of body surface area (see Warnings).

Adriablastina PFS is presently also used extensively in combination chemotherapy at usual doses of 25-50 mg/m² every 3-4 weeks if combined with other myelosuppressive drugs and at doses of 60-75 mg/m² if used in combination with drugs that are not myelosuppressive.

The dosage of Adriablastina PFS should be reduced in patients with impaired hepatic function, to prevent an increase of overall toxicity.

Generally, when serum bilirubin levels are approximately 1.2-3 mg% and BSP retention is 9-15%, it is recommended that half the normal dose of Adriablastina PFS be used. If serum bilirubin levels and BSP retention are even higher, it is recommended that a quarter of the usual dose be given. In view of the low renal excretion of Adriablastina PFS, moderate impairment of renal function does not usually require a reduction in the recommended dose.

It is recommended that Adriablastina PFS be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein, and the dosage. However, the dose should be administered in not less than 3 minutes and not more than 10 minutes to minimize the risk of thrombosis or perivenous extravasation. 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 Warnings). Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Special precautions for storage

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15–25°C).

Handling and disposal

Skin reactions associated with doxorubicin have been reported. Skin accidentally exposed to doxorubicin should be rinsed copiously with soap and warm water, and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published⁽²⁻⁸⁾. There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate.

Preparation of the freeze-dried powder for intravenous administration

Dissolve powder in sodium chloride/water for injection. The vial contents are under negative pressure. To minimize aerosol formation during reconstitution, particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.

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 handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin 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.
- 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 previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

How supplied

Adriablastina PFS (Doxorubicin Hydrochloride Injection, USP)

Single dose vials:

Sterile single use only, contains no preservative.

10 mg vial, 2 mg/mL, 5 mL, single vial packs

50 mg vial, 2 mg/mL, 25 mL, single vial packs

Store under refrigeration, 2° to 8°C. Protect from light. Retain in carton until time of use.

Discard unused portion.

Manufacturer: Pharmacia S.p.A., Milan, Italy

Importer: Agis Commercial Agencies (1989) Ltd., 29 Lehi St., Bnei Brak 51200

License Holder: Pfizer Pharmaceuticals Ltd., 9 Shenkar St., Herzliya Pituach 46725

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