PACKAGE INSERT

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

DOXORUBICIN-SOL PCH 10 mg Solution for Injection

DOXORUBICIN-SOL PCH 20 mg Solution for Injection

DOXORUBICIN-SOL PCH 50 mg Solution for Injection

DOXORUBICIN-SOL PCH 200 mg Solution for Injection

COMPOSITION

Each vial contains 2 mg/ml doxorubicin hydrochloride in a sterile solution for injection.

Excipients: sodium chloride and water for injection.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

There are several hypotheses concerning the mode of action of doxorubicin.

The best documented mechanism is its ability to interact with DNA, presumably by intercalation of the planar aglycon moiety between two adjacent base pairs.

Another mechanism of action may be binding to cell membranes, resulting in altered permeability properties.

A third mechanism involves formation of free-radicals.

There is evidence that free-radical formation may have a role in mutagenicity and cardiotoxicity of doxorubicin.

INDICATIONS

DOXORUBICIN-SOL PCH may be included in combination regimens for the treatment of disseminated neoplastic conditions, such as acute leukaemia, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, lymphomas of both Hodgkin and non-Hodgkin type, small cell lung cancer, gastric carcinoma and bladder carcinoma.

CONTRAINDICATIONS

Hypersensitivity to doxorubicin hydrochloride.

Marked myelosuppression induced by previous chemotherapy or radiotherapy.

Pre-existing heart disease.

Previous treatment with complete cumulative doses of doxorubicin or other anthracyclines.

WARNINGS and SPECIAL PRECAUTIONS

Acute life threatening arrhythmias have been reported to occur during or within a few hours after **DOXORUBICIN-SOL PCH** administration.

Initial treatment with **DOXORUBICIN-SOL PCH** requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients be hospitalized at least during the first phase of the treatment.

DOXORUBICIN-SOL PCH should not be mixed with 5-fluorouracil or heparin. It is not recommended that **DOXORUBICIN-SOL PCH** be mixed with other medicines (see INTERACTIONS).

DOXORUBICIN-SOL PCH should be used only in life-threatening situations.

Doses should not be repeated in patients with bone-marrow depression or with mouth ulcers.

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity.

Gastrointestinal function:

Mucositis (stomatitis and esophagitis) may occur 5 - 10 days after administration. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dose regimen consisting of administration of **DOXORUBICIN-SOL PCH** on three consecutive days results in the greater incidence and severity of mucositis.

Necrotizing colitis manifested by typhlitis (caecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of **DOXORUBICIN-SOL PCH** and cytarabine (see INTERACTIONS).

Cardiac function:

Special attention must be given to the cardiac toxicity exhibited by **DOXORUBICIN-SOL PCH.**

Acute left ventricular failure has occurred, particularly in patients who have received total dosage exceeding the recommended limit of 450-550 mg/m^2. The risk of developing cardiomyopathy increases with increasing doses. The limit appears to be lower in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide, mitomycin C, dacarbazine or other anthracyclines.

Congestive heart failure and/or cardiomyopathy may be encountered several weeks, months or years after discontinuation of **DOXORUBICIN-SOL PCH** therapy. Cardiac failure is often not favourably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of

heart failure is important.

Severe cardiac toxicity may occur precipitously without antecedent electrocardiogram (ECG) changes. A baseline ECG and ECGs should be performed prior to each dose. ECG changes consisting of T-wave flattening, S-T depression and arrhythmias lasting up to two weeks after a dose or course of **DOXORUBICIN-SOL PCH** may occur. **DOXORUBICIN-SOL PCH** cardiomyopathy may be associated with a persistent reduction in the voltage of the QRS wave, a prolongation of the systolic time interval and a reduction of the ejection fraction as determined by echocardiography or radionuclide angiography. If test results indicate change in cardiac function associated with **DOXORUBICIN-SOL PCH** the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage. Long term cardiac monitoring with electrocardiography and echocardiography is recommended.

Haematology:

There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematologic monitoring. Leucopenia is reversible and reaches its nadir at 10 - 14 days after treatment. White blood cell counts as low as 1 000 mm^3 are to be expected during treatment. Red blood cell and platelet levels should also be monitored since they may also be depressed. Haematologic toxicity may require dose reduction or suspension or delay of **DOXORUBICIN-SOL PCH** therapy. Persistent severe myelosuppression may result in super-infection or haemorrhage.

DOXORUBICIN-SOL PCH has mutagenic and immunosuppressant effects which may stimulate the development of neoplasms after prolonged use.

The occurrence of secondary acute myeloid leukemia with or without a pre-leukemic phase has been reported rarely in patients concurrently treated with **DOXORUBICIN-SOL PCH** in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 years) latency period.

Hepatic and renal function:

Abnormal liver function tests may occur in patients using **DOXORUBICIN-SOL PCH**.

Concomitant irradiation of the liver may cause severe hepatotoxicity, sometimes progressing to cirrhosis.

Toxicity is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended.

DOXORUBICIN-SOL PCH may induce hyperuricemia secondary to rapid lysis of neoplastic cells and uric acid nephropathy may occur. Blood uric acid levels should therefore be monitored. **DOXORUBICIN-SOL PCH** may also cause hyperphosphataemia.

Immunosuppressant effects:

Vaccination with live and killed virus should be delayed (recommended period 3-12 months) after completion of treatment.

Dosage and administration related special precautions:

On intravenous administration of **DOXORUBICIN-SOL PCH** extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms or extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein.

Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained. Early wide excision of the involved area should be considered. **DOXORUBICIN-SOL PCH** should not be injected intramuscularly or subcutaneously.

Instructions for use, handling and disposal:

Any contact with solution should be avoided. During preparation and reconstitution a strictly aseptic

working technique should be used; protective measures should include the use of gloves, mask, safety goggles and protective clothing. Use of a vertical laminar airflow (LAF) hood is recommended.

Gloves should be worn during administration. Waste-disposal procedures should take into account the cytotoxic nature of this substance.

If **DOXORUBICIN-SOL PCH** solution contacts skin, mucosae, or eyes, immediately wash thoroughly with water. Soap may be used for skin cleansing. Eyes should be rinsed with saline immediately.

INTERACTIONS

DOXORUBICIN-SOL PCH may potentiate the toxicity of other anticancer therapies.

Exacerbation of cyclophosphamide induced cystitis and enhancement of 6-mercaptopurine hepatotoxicity have been reported.

Radiation induced toxicity to the myocardium, mucosae, skin and liver has been reported to be increased by the administration of **DOXORUBICIN-SOL PCH**.

Inducers of the enzyme cytochrome P-450 (e.g. rifampicin and barbiturates) may stimulate the metabolism of **DOXORUBICIN-SOL PCH**, with a possible decrease in efficacy.

Inhibitors of cytochrome P-450 (e.g. cimetidine) may decrease the metabolism of **DOXORUBICIN-SOL PCH**, with a possible increase in toxic effects.

PREGNANCY AND LACTATION

DOXORUBICIN-SOL PCH is a potentially teratogenic and embryotoxic agent. **DOXORUBICIN-SOL PCH** is excreted into the milk in small amounts.

Usage during pregnancy and lactation should be avoided.

DOSAGE AND DIRECTIONS FOR USE

Patients receiving **DOXORUBICIN-SOL PCH** should be under the care of a physician experienced in

cancer chemotherapy.

The most commonly used dosage schedule is 60 - 75 mg/m^2 as a single intravenous injection administered at 21 day intervals. Lower doses may be required in patients with inadequate marrow reserves. An alternative dosage schedule is 20 mg/m^2 weekly.

DOXORUBICIN-SOL PCH dosage should be reduced if the bilirubin is elevated as follows:

serum bilirubin 21 - 51 μmol/l - give half the normal dose;

serum bilirubin greater than 51 μmol/l - give a quarter of the normal dose.

Admixture with cefalothin sodium, dexamethazone, diazepam and hydrocortisone succinate results in precipitation.

Vascular-phlebosclerosis has been reported especially when small veins are used or a single vein used for repeated administration.

Facial flushing may occur if the injection is given too rapidly.

The total dose of **DOXORUBICIN-SOL PCH** administered to the individual patient should take into account a previous or concomitant therapy with related compounds such as daunorubicin.

DOXORUBICIN-SOL PCH must be used carefully in elderly and debilitated patients and the dose should be reduced in these patients.

DOXORUBICIN-SOL PCH 200 mg is packed as a multi-dose vial, and caution should be exercised to prevent inadvertent overdosage.

It should only be used as a "Pharmacy Bulk Package" and not as a multi-dose vial to be used over a long period.

The risk of development of cardiomyopathy gradually increases with the dosage. A cumulative dose of 550 mg/m^2 should be exceeded.

In general, impaired renal function does not require dose reduction.

DOXORUBICIN-SOL PCH may be given by intravenous bolus injection, or as continuous infusion.

Bolus injection causes higher peak plasma-concentration and therefore is probably more cardiotoxic.

DOXORUBICIN-SOL PCH should not be administered intramuscularly or subcutaneously. Intravenous administration occurs through a running intravenous infusion over three to five minutes.

Patients at increased risk for cardiotoxicity should be considered for treatment with a 24 hours continuous infusion, rather than bolus injection. In this way, cardiotoxicity may be less frequent, without a reduction in therapeutic efficacy. In these patients, the ejection fraction should be measured before each course.

Dosage in children:

Children have an increased risk for late (5-10 years) cardiotoxicity. The maximum recommended cumulative dose is 350 mg/m^2.

SIDE EFFECTS

Skin and subcutaneous tissue disorders:

Frequent: Reversible and complete alopecia occurs in most cases.

Less frequent: Hyperpigmentation of nailbeds and dermal creases, primarily in children, and onycholysis have been reported.

Recall of skin reaction due to prior radiotherapy has occurred with **DOXORUBICIN-SOL PCH** administration.

Gastrointestinal disorders:

Frequent: Acute nausea, vomiting and abdominal pain which may be severe. Mucositis (stomatitis and esophagitis) (see WARNINGS AND SPECIAL PRECAUTIONS).

Less frequent: Ulceration and necrosis of the colon, especially caecum may occur leading to bleeding or

severe infections which can be fatal. Anorexia and diarrhoea have been reported.

General disorders and administration site conditions:

Local

Less frequent: Severe cellulitis, vesication and tissue necrosis will occur if **DOXORUBICIN-SOL PCH** is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported.

General

Less frequent: Weakness, malaise, pulmonary fibrosis, central and peripheral neurotoxicity, headache, hypotension and gynaecomastia may occur.

Immune system disorders:

Frequent: Fever, chills, pruritus and urticaria have been reported.

Less frequent: Anaphylaxis may occur. A case of apparent cross-sensitivity to lidomycin has been reported.

Eye disorders:

Less frequent: Conjunctivitis and lacrimation occur.

Hepato-biliary disorders:

Less frequent: A slight transient increase of liver enzymes have been reported.

Cardiac disorders:

Less frequent: Cardiac toxicity (see WARNINGS AND SPECIAL PRECAUTIONS).

Blood and lymphatic system disorders:

Frequent: Bone marrow depression (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal and urinary disorders:

Less frequent: Hyperuricemia, hyperphosphataemia (see WARNINGS AND SPECIAL PRECAUTIONS).

Frequent: **DOXORUBICIN-SOL PCH** imparts a red coloration to the urine 1 - 2 days after administration.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Acute overdosage of **DOXORUBICIN-SOL PCH** enhances the toxic effects of mucositis, leucopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

Chronic overdosage with cumulative doses exceeding 550 mg/m^2 increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. Cardiac transplants have been performed.

The use of peripheral vasodilators has been recommended.

Myocardial degeneration may occur within 24 hours after an acute overdose.

IDENTIFICATION

A clear red solution.

PRESENTATION

DOXORUBICIN-SOL PCH 10 mg:

5 ml clear glass single dose vial

DOXORUBICIN-SOL PCH 20 mg:

10 ml clear glass single dose vial

DOXORUBICIN-SOL PCH 50 mg:

25 ml clear glass single dose vial

DOXORUBICIN-SOL PCH 200 mg:

100 ml clear glass multi-dose vial

STORAGE INSTRUCTIONS

Store between 2 – 8 ºC and protect from light. Do not freeze the vial.

Store in original package.

After dilution:

After dilution to a concentration of 0,5 mg/ml in 9 mg/ml (0.9 %) sodium chloride solution for infusion or in 50 mg/ml (5 %) glucose solution for infusion, the solution has been shown to be stable for 7 days when stored protected from light at 15 - 25 °C and 2 - 8 °C.

After dilution to the concentration of 0,05 mg/ml, the diluted solution should be used immediately.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

DOXORUBICIN-SOL PCH 10 mg: Z/26/167

DOXORUBICIN-SOL PCH 20 mg: Z/26/168

DOXORUBICIN-SOL PCH 50 mg: Z/26/169

DOXORUBICIN-SOL PCH 200 mg: Z/26/170

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION

Teva Pharmaceuticals (Pty) Ltd

1st Floor, Building 2, Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand,

2090

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 02 July 1996.

Date of revised package insert as per Reg. 9 and 10: 05 February 2016.