

Important Drug Information

Subject: Temporary importation of Doxorubicin Hydrochloride 50 mg Powder for Injection (50 mg/vial) to address drug shortage issue

May 2016

Dear Health Care Provider,

Due to the current critical shortage of Doxorubicin Hydrochloride for Injection, USP in the United States (U.S.) market, Hospira, Inc., a Pfizer company (Hospira), is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of the drug. Hospira has initiated temporary importation of non-U.S. approved product, Doxorubicin Hydrochloride 50 mg Powder for Injection from Hospira Limited, United Kingdom (Hospira Limited): Lot DO21502A, expiration 12/2017.

The Doxorubicin Hydrochloride 50 mg Powder for Injection from Hospira Limited is manufactured by Zydus Hospira Oncology Private Limited (ZHOPL) in Ahmedabad, India, at an FDA-inspected facility that is in compliance with current good manufacturing practice requirements.

At this time, no other entity except Hospira Limited or their distributor Hospira is authorized by the FDA to import or distribute Doxorubicin Hydrochloride 50 mg Powder for Injection in the U.S. FDA has not approved Hospira Limited's Doxorubicin Hydrochloride 50 mg Powder for Injection (50 mg/vial) product in the U.S.

Effective immediately, and during this temporary period, Hospira will offer the following presentation of Doxorubicin Hydrochloride for Injection:

Product	Strength	Size	Marketing Authorization #
Doxorubicin Hydrochloride 50 mg Powder for Injection	50 mg/vial	Box of 1 vial	PL 4515/0073 (United Kingdom)

The barcode used for Hospira Limited's non-U.S. approved Doxorubicin Hydrochloride 50 mg Powder for Injection is an international pharmaceutical manufacturing code and may not be appropriately recognized by scanning systems used in the U.S. Institutions should confirm the barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

It is important to note that there are substantive differences in the format and content of the labeling between the U.S.-approved Doxorubicin Hydrochloride for Injection, USP and the Hospira Limited's Doxorubicin Hydrochloride 50 mg Powder for Injection. The product comparison tables attached highlight the differences between the reference listed drug (RLD) Doxorubicin Hydrochloride for Injection, USP and Hospira Limited's non-U.S. approved Doxorubicin Hydrochloride 50 mg Powder for Injection.

This letter and the attachments are not intended as a complete description of the benefits and risks related to the use of Doxorubicin Hydrochloride 50 mg Powder for Injection. Please refer to the package insert for the FDA-approved Doxorubicin Hydrochloride for Injection, USP for full prescribing information.

To place an order, or if you have any questions, customers can contact Hospira directly by calling Customer Care at 1-877-946-7747 (Monday – Friday, 7AM-6PM CDT).

Hospira will make reasonable attempts to fill your orders. Hospira will be closely monitoring the distribution of Doxorubicin Hydrochloride 50 mg Powder for Injection to help manage supply.

For clinical inquiries, please contact Hospira Medical Communications at 1-800-615-0187 (available 24 hours a day/7 days per week), or email at medcom@hospira.com.

To report adverse events or quality problems associated with the use of this product, please call Hospira Global Complaint Management at 1-800-441-4100 (Monday – Friday, 8AM-5PM CDT), or email at ProductComplaintsPP@hospira.com.

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- Complete and submit the report **Online:** www.fda.gov/medwatch/report.htm.
- **Regular Mail or Fax:** Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

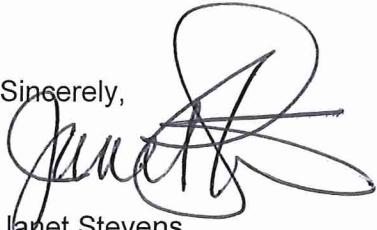
For Full U.S.-approved Prescribing Information for Doxorubicin Hydrochloride for Injection, including the BOXED WARNING, please visit:

<http://www.accessdata.fda.gov/spl/data/bb405a38-3e4e-49af-b30d-fb728f209022/bb405a38-3e4e-49af-b30d-fb728f209022.xml>

For Full Prescribing Information for Hospira Limited's product, please visit:

<http://www.pfizerinjectables.com/sites/default/files/doxorubicinSmPC-HospiraUK.pdf>

Sincerely,



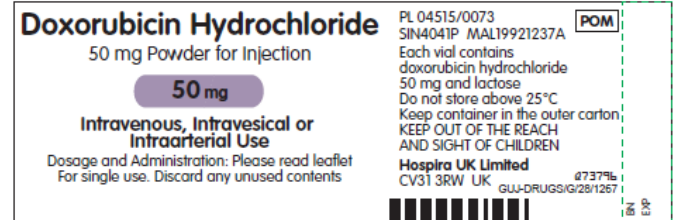
Janet Stevens
Vice President, Quality Operations
Hospira, Inc., a Pfizer Company

Product Vial and Carton Comparison Table

Doxorubicin Hydrochloride for Injection, USP-
doxorubicin hydrochloride injection, powder,
lyophilized, for solution – Reference Listed Drug
(RLD) (Mylan Institutional LLC) Vial Label

Not Available

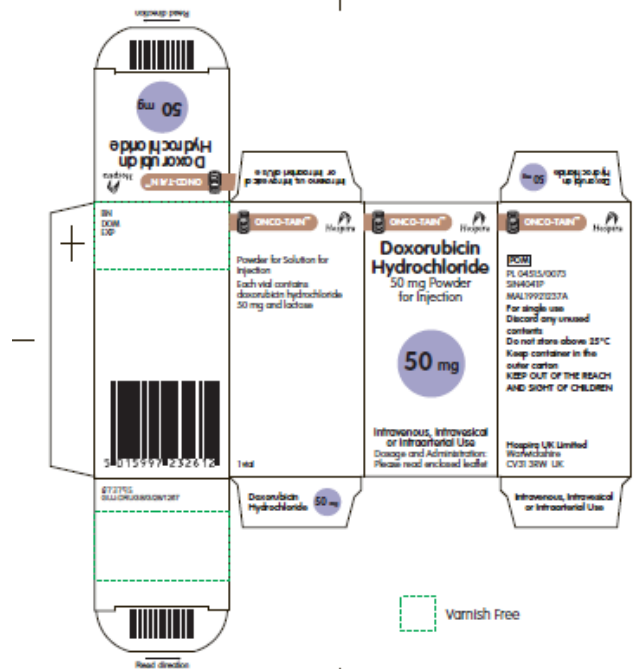
Doxorubicin Hydrochloride 50 mg Powder for
Injection – Hospira Limited Vial Label



Doxorubicin Hydrochloride for Injection, USP-
doxorubicin hydrochloride injection, powder,
lyophilized, for solution – Reference Listed Drug
(RLD) (Mylan Institutional LLC) Carton Label



Doxorubicin Hydrochloride 50 mg Powder for
Injection – Hospira Limited Carton Label



Product Label Comparison Table

<p>Doxorubicin Hydrochloride for Injection, USP - doxorubicin hydrochloride injection, powder, lyophilized, for solution – Reference Listed Drug (RLD) (Mylan Institutional, LLC)</p>	<p>Doxorubicin Hydrochloride 50 mg Powder for Injection – Hospira Limited</p>
<p><i>BOXED WARNING</i></p>	
<p>WARNING: CARDIOMYOPATHY, SECONDARY MALIGNANCIES, EXTRAVASATION AND TISSUE NECROSIS and SEVERE MYELOSUPPRESSION</p> <ul style="list-style-type: none"> • Cardiomyopathy: Myocardial damage, including acute left ventricular failure can occur with doxorubicin hydrochloride. The risk of cardiomyopathy is proportional to the cumulative exposure with incidence rates from 1% to 20% for cumulative doses ranging from 300 mg/m² to 500 mg/m² when doxorubicin hydrochloride is administered every 3 weeks. The risk of cardiomyopathy is further increased with concomitant cardiotoxic therapy. Assess LVEF before and regularly during and after treatment with doxorubicin hydrochloride [see Warnings and Precautions (5.1)]. • Secondary Malignancies : Secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) occur at a higher incidence in patients treated with anthracyclines, including doxorubicin hydrochloride [see Warnings and Precautions (5.2)]. • Extravasation and Tissue Necrosis : Extravasation of doxorubicin hydrochloride can result in severe local tissue injury and necrosis requiring wide excision of the affected area and skin grafting. Immediately terminate the drug and apply ice to the affected area [see Warnings and Precautions (5.3)]. • Severe myelosuppression resulting in serious infection, septic shock, requirement for transfusions , hospitalization, and death may occur [see Warnings and Precautions (5.4)]. 	
<p><i>Indications and contraindications</i></p>	
<p>Doxorubicin hydrochloride, USP is an anthracycline topoisomerase II inhibitor indicated:</p> <ul style="list-style-type: none"> • as a component of multiagent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer. • for the treatment of: acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, metastatic breast cancer, metastatic Wilms' tumor, metastatic neuroblastoma,, metastatic soft tissue sarcoma, metastatic bone sarcomas, metastatic ovarian carcinoma, metastatic transitional cell bladder carcinoma, metastatic thyroid carcinoma, metastatic 	<p>Therapeutic indications Doxorubicin has been used successfully in the treatment of neoplastic conditions such as acute leukaemia, soft tissue and osteogenic sarcomas, breast carcinoma, lymphomas, bronchogenic (lung) carcinoma. It has also been used in the treatment of paediatric malignancy. Doxorubicin is frequently used in combination chemotherapy regimen involving other cytotoxic drugs. Doxorubicin can be used in the treatment of non-metastatic transitional cell carcinoma, carcinoma <i>in situ</i> and papillary tumours of the bladder, by intravesical administration.</p>

Product Label Comparison Table

<p>gastric carcinoma, metastatic bronchogenic carcinoma.</p> <p>Doxorubicin hydrochloride is contraindicated in patients with:</p> <ul style="list-style-type: none"> • Severe myocardial insufficiency [see <i>Warnings and Precautions (5.1)</i>] • Recent (occurring within the past 4-6 weeks) myocardial infarction [see <i>Warnings and Precautions (5.1)</i>] • Severe persistent drug-induced myelosuppression [see <i>Warnings and Precautions (5.4)</i>] • Severe hepatic impairment (defined as Child Pugh Class C or serum bilirubin level greater than 5 mg/dL) [see <i>Warnings and Precautions (5.5)</i>] • Severe hypersensitivity reaction to doxorubicin hydrochloride including anaphylaxis [see <i>Adverse Reactions (6.2)</i>] 	<p>Contraindications</p> <p>Hypersensitivity to doxorubicin or any of the excipients.</p> <p>Dosage should not be repeated in cases of bone marrow depression or buccal ulceration or buccal burning sensation, which can precede ulceration.</p>
<p><i>Dosage and Administration</i></p>	
<p>Recommended Dose</p> <p><i>Adjuvant Breast Cancer</i></p> <p>The recommended dose of doxorubicin hydrochloride, USP is 60 mg/m² administered as an intravenous bolus on day 1 of each 21-day treatment cycle, in combination with cyclophosphamide, for a total of four cycles [see <i>Clinical Studies (14)</i>].</p> <p><i>Metastatic Disease, Leukemia, or Lymphoma</i></p> <ul style="list-style-type: none"> • The recommended dose of doxorubicin hydrochloride, USP when used as a single agent is 60 to 75 mg/m² intravenously every 21 days. • The recommended dose of doxorubicin hydrochloride, USP, when administered in combination with other chemotherapy drugs, is 40 to 75 mg/m² intravenously every 21 to 28 days. • Consider use of the lower doxorubicin dose in the recommended dose range or longer intervals between cycles for heavily pretreated patients, elderly patients, or obese patients. • Cumulative doses above 550 mg/m² are associated with an increased risk of cardiomyopathy [see <i>Warnings and Precautions (5.1)</i>]. <p>Dose Modifications</p> <p><i>Cardiac Impairment</i></p> <p>Discontinue doxorubicin in patients who develop signs or symptoms of cardiomyopathy.</p> <p><i>Hepatic Impairment</i></p> <p>Doxorubicin hydrochloride, USP is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C or serum bilirubin >5.0 mg/dL) [see <i>Contraindications (4)</i>].</p>	<p><u>Intravenous administration</u></p> <p>When used as a single agent, the recommended dosage is 60-75 mg/m² body surface area, as a single intravenous injection administered at 21 day intervals. If it is used in combination with other antitumour agents having overlapping toxicity, the dosage for doxorubicin may need to be reduced to 30-40 mg/m² every three weeks. If using body weight to calculate the dose, then dosages of 1.2 – 2.4 mg/kg as a single dose every three weeks are recommended.</p> <p>It has been shown that giving doxorubicin as a single dose every three weeks greatly reduces the distressing toxic effect, mucositis. However, there are some regimens which divide the dose over three successive days (20-25 mg/m² or 0.4-0.8 mg/kg). It is thought that this regimen has greater effectiveness although at a cost of higher toxicity.</p> <p>Administration of doxorubicin in a weekly regimen has been shown to be as effective as the three weekly regimen. The recommended dosage is 20 mg/m² once a week although objective responses have been seen at 6-12 mg/m². This regimen of weekly dosing also reduces the incidence of cardiotoxicity.</p> <p>It is particularly important to reduce the dose of doxorubicin if it is used in combination with other drugs with a similar toxicity profile. The recommended lifetime cumulative dose limit is 450-550 mg doxorubicin hydrochloride/m² body surface area.</p>

Product Label Comparison Table

<p>Decrease the dose of doxorubicin hydrochloride, USP in patients with elevated serum total bilirubin concentrations as follows:</p>	<p>It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection 0.9% or 5% Dextrose Injection. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. 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 to 5 minutes. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.</p>								
<table border="1"> <thead> <tr> <th data-bbox="181 344 496 436">Serum bilirubin concentration</th> <th data-bbox="496 344 797 436">Doxorubicin hydrochloride, USP Dose reduction</th> </tr> </thead> <tbody> <tr> <td data-bbox="181 436 496 470">1.2 to 3 mg/dL</td> <td data-bbox="496 436 797 470">50 %</td> </tr> <tr> <td data-bbox="181 470 496 504">3.1 to 5 mg/dL</td> <td data-bbox="496 470 797 504">75 %</td> </tr> <tr> <td data-bbox="181 504 496 684">greater than 5 mg/dL</td> <td data-bbox="496 504 797 684">Do not initiate doxorubicin hydrochloride, USP Discontinue doxorubicin hydrochloride, USP</td> </tr> </tbody> </table>	Serum bilirubin concentration	Doxorubicin hydrochloride, USP Dose reduction	1.2 to 3 mg/dL	50 %	3.1 to 5 mg/dL	75 %	greater than 5 mg/dL	Do not initiate doxorubicin hydrochloride, USP Discontinue doxorubicin hydrochloride, USP	<p>Intravenous infusion is not advised due to the tissue damage that may occur if the infusion infiltrates the tissues. If a central vein catheter is used then infusion of doxorubicin in Sodium Chloride 0.9% Injection is advised.</p>
Serum bilirubin concentration	Doxorubicin hydrochloride, USP Dose reduction								
1.2 to 3 mg/dL	50 %								
3.1 to 5 mg/dL	75 %								
greater than 5 mg/dL	Do not initiate doxorubicin hydrochloride, USP Discontinue doxorubicin hydrochloride, USP								
<p>[see Warnings and Precautions (5.5) and Use in Specific Populations (8.7)]</p>	<p>Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Please refer to section 6.2 for details on incompatibilities.</p>								
<p>Preparation and Administration</p>	<p><u>Intravesical administration</u></p>								
<p><i>Preparation of Doxorubicin Hydrochloride for injection, USP</i></p>	<p>This technique may be used for the treatment of transitional cell carcinoma, papillary bladder tumours and carcinoma <i>in situ</i>. It should not be used for invasive tumours of the bladder which have penetrated the bladder wall.</p>								
<p>Reconstitute doxorubicin hydrochloride for injection, USP with 0.9% Sodium Chloride Injection, USP to obtain a final concentration of 2 mg per mL as follows:</p>	<p>Many regimens are in use, making interpretation difficult, but the following procedure may be a helpful guide:</p>								
<ul style="list-style-type: none"> • 5 mL 0.9% Sodium Chloride Injection, USP to reconstitute 10 mg doxorubicin hydrochloride, USP vial. • 25 mL 0.9% Sodium Chloride Injection, USP to reconstitute 50 mg doxorubicin hydrochloride, USP vial. 	<ol style="list-style-type: none"> 1. Patient should be instructed not to drink fluids for 12 hours prior to the examination. 2. Dissolve 50 mg of doxorubicin in 50 ml of normal saline and instil via the catheter into the bladder. 3. The catheter should be removed and the patient instructed to be on one side. At 15 minute intervals the patient should make a quarter turn over a 1 hour period. At the end of this period, the patient may void. 4. The procedure may be repeated at monthly intervals. 								
<p>Gently shake vial until the contents have dissolved.</p>	<p><u>Intraarterial administration</u></p>								
<p>Protect reconstituted solution from light.</p>	<p>Doxorubicin hydrochloride has been administered as an intra-arterial infusion in an attempt to produce local intense activity and reduce systemic toxicity. However it must be recognised that this route of administration is potentially extremely hazardous and can lead to</p>								
<p><i>Administration</i></p>									
<p>Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if the solution is discolored, cloudy, or contains particulate matter.</p>									
<p>Storage of vials of Doxorubicin hydrochloride for injection, USP following reconstitution under refrigerated conditions can result in the formation of a gelled product. Place gelled product at room temperature [15° to 30° C (59° to 86° F)] for 2 to 4 hours to return the product to a slightly viscous, mobile solution.</p>									
<p><i>Administration by Intravenous Injection:</i></p>									
<ul style="list-style-type: none"> • Administer doxorubicin hydrochloride, USP as an 									

Product Label Comparison Table

<p>intravenous injection through a central intravenous line or a secure and free-flowing peripheral venous line containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.</p> <ul style="list-style-type: none"> Administer doxorubicin hydrochloride, USP intravenously over 3 to 10 minutes. Decrease the rate of doxorubicin hydrochloride, USP administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. <p><i>Administration by Continuous Intravenous Infusion:</i> Infuse only through a central catheter. Decrease the rate of doxorubicin hydrochloride, USP administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.</p> <p>Protect from light from preparation for infusion until completion of infusion.</p> <ul style="list-style-type: none"> Infuse only through a central catheter. Decrease the rate of doxorubicin hydrochloride, USP administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur. Protect from light from preparation for infusion until completion of infusion. <p><i>Management of Suspected Extravasation</i> Discontinue doxorubicin hydrochloride, USP for burning or stinging sensation or other evidence indicating perivenous infiltration or extravasation. Manage confirmed or suspected extravasation as follows:</p> <ul style="list-style-type: none"> Do not remove the needle until attempts are made to aspirate extravasated fluid. Do not flush the line. Avoid applying pressure to the site. Apply ice to the site intermittently for 15 min 4 times a day for 3 days. If the extravasation is in an extremity, elevate the extremity. In adults, consider administration of dexrazoxane [see <i>Warnings and Precautions (5.3)</i>]. <p><i>Incompatibility with Other Drugs</i> Do not admix doxorubicin hydrochloride, USP with other drugs. If doxorubicin hydrochloride, USP is mixed with heparin or fluorouracil a precipitate may form. Avoid contact with alkaline solutions which can lead to hydrolysis of doxorubicin hydrochloride, USP.</p>	<p>widespread necrosis of perfused tissue unless careful precautions are taken. Intraarterial administration should be undertaken only by experienced professionals.</p> <p><u>Paediatric</u> Adult dosage regimens may be suitable for paediatric cases, but may need to be reduced.</p> <p><u>Geriatric</u> It is recommended that the total cumulative dose of doxorubicin for adults aged 70 or older be restricted to 450 mg/m² body surface area. Adult doses may be suitable for geriatric patients, but may need to be reduced.</p> <p><u>Impaired Hepatic Function</u> Doxorubicin is metabolised by the liver and excreted in bile. Impairment of liver function results in slower excretion of the drug and consequently increased retention and accumulation in the plasma and tissues, resulting in enhanced clinical toxicity.</p> <p>Doxorubicin dosage must be reduced if hepatic function is impaired according to the following table:</p> <table border="1" data-bbox="823 1014 1429 1201"> <thead> <tr> <th>Serum Bilirubin Levels</th> <th>BSP Retention</th> <th>Recommended Dose</th> </tr> </thead> <tbody> <tr> <td>20-50 micromol/L</td> <td>9 – 15%</td> <td>50% normal dose</td> </tr> <tr> <td>Over 50 micromol/L</td> <td>Over 15%</td> <td>25% normal dose</td> </tr> </tbody> </table> <p><u>Impaired Renal Function</u> Doxorubicin and metabolites are excreted in the urine to a minor degree and there are no clear indications that the pharmacokinetics or toxicity of doxorubicin are altered in patients with impaired renal function.</p> <p><u>Incompatibilities</u> Doxorubicin should not be mixed with heparin 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.</p>	Serum Bilirubin Levels	BSP Retention	Recommended Dose	20-50 micromol/L	9 – 15%	50% normal dose	Over 50 micromol/L	Over 15%	25% normal dose
Serum Bilirubin Levels	BSP Retention	Recommended Dose								
20-50 micromol/L	9 – 15%	50% normal dose								
Over 50 micromol/L	Over 15%	25% normal dose								

Product Label Comparison Table

<p>Procedures for Proper Handling and Disposal Handle and dispose of doxorubicin hydrochloride, USP consistent with recommendations for the handling and disposal of hazardous drugs.</p> <p>Treat accidental contact with the skin or eyes immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution. Do not abrade the skin by using a scrub brush. Seek medical attention.</p>	
<i>Warnings</i>	
<p>Cardiomyopathy and Arrhythmias</p> <p>Cardiomyopathy Doxorubicin hydrochloride can result in myocardial damage, including acute left ventricular failure. The risk of cardiomyopathy is generally proportional to the cumulative exposure. Include prior doses of other anthracyclines or anthracenediones in calculations of total cumulative dosage for doxorubicin hydrochloride. Cardiomyopathy may develop during treatment or up to several years after completion of treatment and can include decrease in LVEF and signs and symptoms of congestive heart failure (CHF). The probability of developing cardiomyopathy is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m² of doxorubicin hydrochloride, 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, when doxorubicin hydrochloride is administered every 3 weeks. There is an additive or potentially synergistic increase in the risk of cardiomyopathy in patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents such as cyclophosphamide and trastuzumab.</p> <p>Pericarditis and myocarditis have also been reported during or following doxorubicin hydrochloride treatment.</p> <p>Assess left ventricular cardiac function (e.g., MUGA or echocardiogram) prior to initiation of doxorubicin hydrochloride, during treatment to detect acute changes, and after treatment to detect delayed cardiotoxicity. Increase the frequency of assessments as the cumulative dose exceeds 300 mg/m². Use the same method of assessment of LVEF at all time points [see <i>Use in Specific Populations</i> (8.4)].</p> <p>Consider the use of dexrazoxane to reduce the incidence and severity of cardiomyopathy due to doxorubicin hydrochloride administration in patients who have received a cumulative doxorubicin hydrochloride dose of 300 mg/m² and who will continue to receive doxorubicin hydrochloride.</p>	<p>Experienced Physician: Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.</p> <p>Cardiac Toxicity: Special attention must be given to the cardiac toxicity exhibited by doxorubicin. This may present as tachycardia or ECG changes including supraventricular tachycardia. Severe cardiac failure may occur suddenly, without premonitory ECG changes.</p> <p>It is recommended that the cumulative total lifetime dose of doxorubicin (including related drugs such as daunorubicin) should not exceed 450 – 550 mg/m² body surface area. Above this dosage, the risk of irreversible congestive cardiac failure increases greatly. Total dose should also take account of any previous or concomitant mediastinal irradiation, other anthracycline chemotherapy or concurrent high dose cyclophosphamide, which may also exhibit cardiotoxic effects.</p> <p>Congestive heart failure and/or cardiomyopathy may occur even years after discontinuation of doxorubicin therapy. For this reason extreme care should be taken in patients with existing associated heart disease.</p> <p>Cardiac failure is often not favourably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent ECG changes. Base line ECG and periodic follow up ECG during and immediately after active drug therapy is an advisable precaution. Transient ECG changes, such as T-wave flattening, S-T depression and arrhythmias are not considered indications for suspension of doxorubicin therapy. A persistent reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.</p>

Product Label Comparison Table

<p>Arrhythmias Doxorubicin hydrochloride can result in arrhythmias, including life-threatening arrhythmias, during or within a few hours after doxorubicin hydrochloride administration and at any time point during treatment. Tachyarrhythmias, including sinus tachycardia, premature ventricular contractions, and ventricular tachycardia, as well as bradycardia may occur. Electrocardiographic changes including non-specific ST-T wave changes, atrioventricular and bundle-branch block can also occur. These electrocardiographic changes may be transient and self-limited and may not require dose-modifications of doxorubicin hydrochloride.</p> <p>Secondary Malignancies The risk of developing secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) is increased following treatment with doxorubicin hydrochloride. Cumulative incidences ranged from 0.2% at five years to 1.5% at 10 years in two separate trials involving the adjuvant treatment of women with breast cancer. These leukemias generally occur within 1 to 3 years of treatment.</p> <p>Extravasation and Tissue Necrosis Extravasation of doxorubicin hydrochloride can result in severe local tissue injury manifesting as blistering, ulceration, and necrosis requiring wide excision of the affected area and skin grafting. When given via a peripheral venous line, infuse doxorubicin over 10 minutes or less to minimize the risk of thrombosis or perivenous extravasation. If signs or symptoms of extravasation occur, immediately terminate the injection or infusion [see <i>Dosage and Administration (2.3)</i>]. Extravasation may be present in patients who do not experience a stinging or burning sensation or when blood return is present on aspiration of the infusion needle. If extravasation is suspected, apply ice to the site intermittently for 15 minutes, 4 times a day for 3 days. If appropriate, administer dexrazoxane at the site of extravasation as soon as possible and within the first 6 hours after extravasation.</p> <p>Severe Myelosuppression Doxorubicin hydrochloride can cause myelosuppression. In Study 1, the incidence of severe myelosuppression was: grade 4 leukopenia (0.3%), grade 3 leukopenia (3%), and grade 4 thrombocytopenia (0.1%). A dose-dependent, reversible neutropenia is the predominant manifestation of hematologic toxicity from doxorubicin hydrochloride. When doxorubicin hydrochloride is administered every 21 days, the neutrophil count reaches its nadir 10 to 14 days after administration with recovery usually occurring by the 21st day. Obtain baseline assessment of blood counts and</p>	<p>The best non-invasive predictor of cardiomyopathy is a reduction in the left ventricular ejection fraction (LVEF), determined by ultra-sound or heart scintigraphy. LVEF–investigations are highly recommended before treatment and should be repeated after an accumulated dose of about 350-400 mg/m² in patients with normal cardiac function at baseline. Also repeat if there are clinical signs of heart failure at any cumulative dose. As a rule, an absolute decrease of $\geq 10\%$ or a decrease to below 50% in patients with normal initial LVEF values, is a sign of impairment of cardiac function. Continued treatment with doxorubicin must be carefully evaluated in these cases.</p> <p>Bone Marrow Depression: There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. With the recommended dosage schedule, leucopenia is usually transient, reaching its nadir at 10 – 14 days after treatment, with recovery usually occurring by the 21st day. White blood cell 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.</p> <p>Haematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy.</p> <p>Immunosuppression: Doxorubicin is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection.</p> <p>Severe Myelosuppression: Persistent severe myelosuppression may result in superinfection or haemorrhage.</p> <p>Enhanced Toxicity: It has been reported that doxorubicin may enhance the severity of the toxicity of anticancer therapies, such as cyclophosphamide induced haemorrhagic cystitis, mucositis induced by radiotherapy and hepatotoxicity of 6-mercaptopurine.</p> <p>Infertility: Doxorubicin may cause infertility during the time of drug administration. Although ovulation and menstruation appear to return after termination of therapy, there is no information about the restoration of male fertility.</p>
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Product Label Comparison Table

<p>carefully monitor patients during treatment for possible clinical complications due to myelosuppression.</p> <p>Use in Patients with Hepatic Impairment The clearance of doxorubicin is decreased in patients with elevated serum bilirubin with an increased risk of toxicity [see <i>Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)</i>]. Reduce the dose of doxorubicin hydrochloride in patients with serum bilirubin levels of 1.2 to 5 mg/dL [see <i>Dosage and Administration (2.2)</i>]. Doxorubicin is contraindicated in patients with severe hepatic impairment (defined as Child Pugh Class C or serum bilirubin level greater than 5 mg/dL) [see <i>Contraindications (4)</i>]. Obtain liver tests including SGOT, SGPT, alkaline phosphatase, and bilirubin prior to and during doxorubicin hydrochloride therapy.</p> <p>Tumor Lysis Syndrome Doxorubicin hydrochloride may induce tumor lysis syndrome in patients with rapidly growing tumors. Evaluate blood uric acid levels, potassium, calcium, phosphate, and creatinine after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor lysis syndrome.</p> <p>Radiation Sensitization and Radiation Recall Doxorubicin hydrochloride can increase radiation-induced toxicity to the myocardium, mucosa, skin, and liver. Radiation recall, including but not limited to cutaneous and pulmonary toxicity, can occur in patients who receive doxorubicin hydrochloride after prior radiation therapy.</p> <p>Embryofetal Toxicity Doxorubicin hydrochloride can cause fetal harm when administered to a pregnant woman. Doxorubicin hydrochloride was teratogenic and embryotoxic in rats and rabbits at doses lower than the recommended human dose.</p> <p>If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus [see <i>Use in Specific Populations (8.1)</i>].</p> <p>Advise female patients of reproductive potential to use highly effective contraception during treatment with doxorubicin hydrochloride and for 6 months after treatment. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking doxorubicin hydrochloride [see <i>Use in Specific Populations (8.1) and (8.6)</i>].</p>	<p>Hepatic Impairment: Toxicity to recommended doses of doxorubicin is enhanced by hepatic impairment. It is recommended that an evaluation of hepatic function be carried out prior to individual dosing, using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase, bilirubin and BSP. If required, dosage schedules should be reduced accordingly (see section 4.2).</p> <p>Extravasation: On intravenous administration of doxorubicin, a stinging or burning sensation signifies extravasation and, even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein.</p> <p>Should extravasation occur, stop the infusion immediately and apply ice packs to the injection site. Local injection of dexamethasone or hydrocortisone may be used to minimize local tissue necrosis. Hydrocortisone cream 1% may also be applied locally.</p>
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Product Label Comparison Table

<i>Storage and Handling</i>	
<p>Store unreconstituted vial at controlled room temperature, between 20°C to 25°C (68°F to 77°F). [See USP.] Protect vials from light. Retain in carton until time of use. Discard unused portion.</p> <p>Reconstituted Solution Stability After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light (100 footcandles) and 15 days under refrigeration (2° to 8°C). It should be protected from exposure to sunlight. Discard any unused solution from the 10 mg and 50 mg single dose vials.</p>	<p>Prior to first use: Do not store above 25°C. Keep container in the outer carton.</p> <p>In use: Chemical and physical in-use stability following reconstitution in either sodium chloride 0.9% or Water for Injections in glass or polypropylene containers has been demonstrated for up to 21 days at 2-8°C. From a microbiological point of view, however, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours when stored at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions</p> <p>Single use only. Discard any unused contents. Doxorubicin is a potent cytotoxic agent which should only be prescribed, prepared and administered by professionals who have been trained in the safe use of the preparation. The following guidelines should be followed when handling, preparing and disposing of doxorubicin.</p> <p>Preparation</p> <ol style="list-style-type: none">1. Reconstitution of powder, transfer to syringes or infusion bags should be carried out in designated areas, preferably a laminar flow station.2. Personnel must be adequately protected with suitable clothing, gloves, mask and eye shield.3. Pregnant women should be excluded from handling cytotoxic agents. <p>Preparation of the Injection The contents of the vial should be reconstituted with Water for Injection BP, Sodium Chloride 0.9%, or Dextrose 5% Injection to a solution concentration of 2 mg per ml.</p> <p>Contamination</p> <ol style="list-style-type: none">1. In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat transient stinging of skin. Medical advice should be sought if the eyes are affected.2. In the event of spillage treat with 1% Sodium Hypochlorite solution using a cloth/sponge kept in the designate area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

Product Label Comparison Table

<p>Handling and Disposal Handle and dispose of Doxorubicin Hydrochloride for Injection, USP consistent with recommendations for the handling and disposal of hazardous drugs.</p>	<p>Disposal All items used during preparation or administration including syringes, containers, absorbent materials, residual solutions should all be placed in a thick plastic bag and incinerated at 700°C.</p>
<i>How supplied</i>	
<p>50 mg vial; individually boxed NDC 67457-436-50</p>	<p>1 x 50 mg vial Authorization #PL 4515/0073</p>
<i>Revision Date</i>	
<p>March 2014</p>	<p>January 2008</p>
<i>Barcode</i>	
<p>A unit of use barcode is on individual units.</p>	<p>Barcode use by DOXORUBICIN HYDROCHLORIDE 50 mg Powder for Injection may not register accurately in the United States scanning systems. Alternate procedures should be followed to assure that the correct drug product is being used and administered to individual patients.</p>
<i>Additional information</i>	
<p>N/A</p>	<p>Contains a patient information leaflet</p>