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2 **Doxorubicin Hydrochloride for Injection, USP**

3

4 **Doxorubicin Hydrochloride Injection, USP**

5

6 **Rx Only**

7

8 **FOR INTRAVENOUS USE ONLY**

9

10 **WARNING**

11 1. Severe local tissue necrosis will occur if there is extravasation during administration (see  
12 DOSAGE AND ADMINISTRATION). Doxorubicin must not be given by the intramuscular  
13 or subcutaneous route.

14 2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive  
15 heart failure may occur either during therapy or months to years after termination of therapy.  
16 The probability of developing impaired myocardial function based on a combined index of  
17 signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1  
18 to 2% at a total cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin, 3 to 5% at a dose of 400  
19 mg/m<sup>2</sup>, 5 to 8% at 450 mg/m<sup>2</sup> and 6 to 20% at 500 mg/m<sup>2</sup>. The risk of developing CHF  
20 increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400  
21 mg/m<sup>2</sup>. Risk factors (active or dormant cardiovascular disease, prior or concomitant  
22 radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines  
23 or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of  
24 cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses  
25 whether or not cardiac risk factors are present. Pediatric patients are at increased risk for  
26 developing delayed cardiotoxicity.

27 3. Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) has  
28 been reported in patients treated with anthracyclines, including doxorubicin (see ADVERSE  
29 REACTIONS). The occurrence of refractory secondary AML or MDS is more common  
30 when anthracyclines are given in combination with DNA-damaging anti-neoplastic agents or  
31 radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses  
32 of anthracyclines have been escalated. The rate of developing secondary AML or MDS has

33 been estimated in an analysis of 8563 patients with early breast cancer treated in 6 studies  
34 conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including  
35 NSABP B-15. Patients in these studies received standard doses of doxorubicin and standard  
36 or escalated doses of cyclophosphamide (AC) adjuvant chemotherapy and were followed for  
37 61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11  
38 cases of AML or MDS were identified, for an incidence of 0.32 cases per 1000 patient years  
39 (95% CI 0.16-0.57) and a cumulative incidence at 5 years of 0.21% (95% CI 0.11-.41%). In  
40 another analysis of 1474 patients with breast cancer who received adjuvant treatment with  
41 doxorubicin-containing regimens in clinical trials conducted at University of Texas M.D.  
42 Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In both  
43 experiences, patients who received regimens with higher cyclophosphamide dosages, who  
44 received radiotherapy, or who were aged 50 or older had an increased risk of secondary AML  
45 or MDS. Pediatric patients are also at risk of developing secondary AML.

46 4. Dosage should be reduced in patients with impaired hepatic function.

47 5. Severe myelosuppression may occur.

48 6. Doxorubicin should be administered only under the supervision of a physician who is  
49 experienced in the use of cancer chemotherapeutic agents.

## 52 DESCRIPTION

53 Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces*  
54 *peucetius* var. *caesius*. Doxorubicin consists of a naphthacenequinone nucleus linked through  
55 a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. Chemically, doxorubicin  
56 hydrochloride is: 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy- $\alpha$ -L-lyxo-  
57 hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-,  
58 hydrochloride (8S-*cis*)-. The structural formula is as follows:

60 [INSERT STRUCTURE]

62 Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar  
63 anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but  
64 the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino

65 sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic  
66 functions in the ring phenolic groups and a basic function in the sugar amino group. It binds  
67 to cell membranes as well as plasma proteins.

68

69 Doxorubicin Hydrochloride for Injection, USP, is a sterile red-orange lyophilized powder.

70

71 Doxorubicin Hydrochloride Injection, USP, is a sterile parenteral, isotonic solution.

72

73

#### 74 **CLINICAL PHARMACOLOGY**

75 The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs  
76 are thought to be related to nucleotide base intercalation and cell membrane lipid binding  
77 activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and  
78 RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-  
79 cleavable complexes appears to be an important mechanism of doxorubicin cytotoxic  
80 activity.

81

82 Doxorubicin cellular membrane binding may affect a variety of cellular functions.

83 Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and  
84 dehydrogenases generates highly reactive species including the hydroxyl free radical  $\text{OH}\cdot$ .

85 Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II)  
86 and Fe (III) reduction at the cellular level.

87

88 Cells treated with doxorubicin have been shown to manifest the characteristic morphologic  
89 changes associated with apoptosis or programmed cell death. Doxorubicin-induced  
90 apoptosis may be an integral component of the cellular mechanism of action relating to  
91 therapeutic effects, toxicities, or both.

92

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

97

98 **Pharmacokinetics**

99 Pharmacokinetic studies, determined in patients with various types of tumors undergoing  
100 either single or multi-agent therapy have shown that doxorubicin follows a multiphasic  
101 disposition after intravenous injection. In four patients, doxorubicin has demonstrated dose-  
102 independent pharmacokinetics in the dose range of 30 to 70 mg/m<sup>2</sup>.

103

104 *Distribution.* The initial distribution half-life of approximately 5 minutes suggests rapid  
105 tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a  
106 terminal half-life of 20 to 48 hours. Steady-state distribution volume ranges from 809 to  
107 1214 L/m<sup>2</sup> and is indicative of extensive drug uptake into tissues. Binding of doxorubicin  
108 and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is  
109 independent of plasma concentration of doxorubicin up to 1.1 µg/mL.

110

111 Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration  
112 at 24 hours after treatment being approximately 4.4-fold greater than the corresponding  
113 plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy  
114 with 70 mg/m<sup>2</sup> of doxorubicin given as a 15-minute intravenous infusion and 100 mg/m<sup>2</sup> of  
115 cisplatin as a 26-hour intravenous infusion. The peak concentration of doxorubicinol in milk  
116 at 24 hours was 0.11 µg/mL and AUC up to 24 hours was 9.0 µg.h/mL while the AUC for  
117 doxorubicin was 5.4 µg.h/mL.

118

119 Doxorubicin does not cross the blood brain barrier.

120

121 *Metabolism.* Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar  
122 yields aglycones which are accompanied by free radical formation, the local production of  
123 which may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol  
124 (DOX-OL) in patients is formation rate limited, with the terminal half-life of DOX-OL being  
125 similar to doxorubicin. The relative exposure of DOX-OL, i.e., the ratio between the AUC of  
126 DOX-OL and the AUC of doxorubicin, compared to doxorubicin ranges between 0.4 and 0.6.

127

128 *Excretion.* Plasma clearance is in the range 324 to 809 mL/min/m<sup>2</sup> and is predominately by  
129 metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5  
130 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same  
131 time period. In urine, <3% of the dose was recovered as DOX-OL over 7 days.

132

133 Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body  
134 weight greater than 130%. There was a significant reduction in clearance without any  
135 change in volume of distribution in obese patients when compared with normal patients with  
136 less than 115% ideal body weight.

137

### 138 **Pharmacokinetics in Special Populations**

139 *Pediatric.* Following administration of 10 to 75-mg/m<sup>2</sup> doses of doxorubicin to 60 children  
140 and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged  
141 1443 ± 114 mL/min/m<sup>2</sup>. Further analysis demonstrated that clearance in 52 children greater  
142 than 2 years of age (1540 mL/min/m<sup>2</sup>) was increased compared with adults. However,  
143 clearance in infants younger than 2 years of age (813 mL/min/m<sup>2</sup>) was decreased compared  
144 with older children and approached the range of clearance values determined in adults.

145 *Geriatric.* While the pharmacokinetics of elderly subjects (≥65 years of age) have been  
146 evaluated, no dosage adjustment is recommended based on age. (See PRECAUTIONS,  
147 Geriatric Use.)

148 *Gender.* A published clinical study involving 6 men and 21 women with no prior  
149 anthracycline therapy reported a significantly higher median doxorubicin clearance in the  
150 men compared to the women (1088 mL/min/m<sup>2</sup> versus 433 mL/min/m<sup>2</sup>). However, the  
151 terminal half-life of doxorubicin was longer in men compared to the women (54 versus 35  
152 hours).

153 *Race.* The influence of race on the pharmacokinetics of doxorubicin has not been evaluated.

154 *Hepatic Impairment.* The clearance of doxorubicin and doxorubicinol was reduced in patients  
155 with impaired hepatic function (see DOSAGE & ADMINISTRATION).

156 *Renal Impairment.* The influence of renal function on the pharmacokinetics of doxorubicin  
157 has not been evaluated.

158

159

160 **CLINICAL STUDIES**

161 The effectiveness of doxorubicin-containing regimens in the adjuvant therapy of early breast  
162 cancer has primarily been established based on data collected in a meta-analysis published in  
163 1998 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG). The EBCTCG  
164 obtains primary data on all relevant studies, both published and unpublished, for early stage  
165 breast cancer and regularly updates these analyses. The principal endpoints for the adjuvant  
166 chemotherapy trials were disease-free survival (DFS) and overall survival (OS). The meta-  
167 analyses allowed comparisons of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)  
168 to no chemotherapy (19 trials including 7523 patients) and comparisons of doxorubicin-  
169 containing regimens with CMF as an active control (6 trials including 3510 patients). The  
170 pooled estimates of DFS and OS from these trials were used to calculate the effect of CMF  
171 relative to no therapy. The hazard ratio for DFS for CMF compared to no chemotherapy was  
172 0.76 (95% CI 0.71-0.82) and for OS was 0.86 (95% CI 0.80-0.93). Based on a conservative  
173 estimate of CMF effect (lower 2-sided 95% confidence limit of hazard ratio) and 75%  
174 retention of CMF effect on DFS, it was determined that the doxorubicin containing-regimens  
175 would be considered as non-inferior to CMF if the upper 2-sided 95% confidence limit of the  
176 hazard ratio was less than 1.06, i.e. not more than 6% worse than CMF. A similar calculation  
177 for OS would require a non-inferiority margin of 1.02.

178

179 Six randomized trials in the EBCTCG meta-analysis compared doxorubicin-containing  
180 regimens to CMF. A total of 3510 women with early breast cancer involving axillary lymph  
181 nodes were evaluated; approximately 70% were premenopausal and 30% were  
182 postmenopausal. At the time of the meta-analysis, 1745 first recurrences and 1348 deaths  
183 had occurred. Analyses demonstrated that doxorubicin-containing regimens retained at least  
184 75% of the historical CMF adjuvant effect on DFS and are effective. The hazard ratio for  
185 DFS (dox:CMF) was 0.91 (95% CI 0.82-1.01) and for OS was 0.91 (95% CI 0.81-1.03).  
186 Results of these analyses for both DFS and OS are provided in Table 1 and Figures 1 and 2.

187

**Table 1. Summary of Randomized Trials Comparing Doxorubicin-Containing Regimens Versus CMF in EBCTCG Meta-Analysis**

Study (starting year)	Regimens	No. of Cycles	No. of Patients	Doxorubicin-Containing Regimens vs CMF HR (95% CI)	
				DFS	OS
NSABP B-15 (1984)	AC	4	1562*	0.93 (0.82-1.06)	0.97 (0.83-1.12)
	CMF	6	776		
SECSG 2 (1976)	FAC	6	260	0.86 (0.66-1.13)	0.93 (0.69-1.26)
	CMF	6	268		
ONCOFRANCE (1978)	FACV	12	138	0.71 (0.49-1.03)	0.65 (0.44-0.96)
	CMF	12	113		
SE Sweden BCG A (1980)	AC	6	21	0.59 (0.22-1.61)	0.53 (0.21-1.37)
	CMF	6	22		
NSABC Israel Br0283 (1983)	AVb†	4	55	0.91 (0.53-1.57)	0.88 (0.47-1.63)
	CMF	6	50		
	CMF	6	50		
Austrian BCSG 3 (1984)	CMFVA	6	121	1.07 (0.73-1.55)	0.93 (0.64-1.35)
	CMF	8	124		
<b>Combined Studies</b>	Doxorubicin-Containing Regimens		<b>2157</b>	<b>0.91 (0.82-1.01)</b>	<b>0.91 (0.81-1.03)</b>
	CMF		<b>1353</b>		

**Abbreviations:** DFS = disease free survival; OS = overall survival; AC = doxorubicin, cyclophosphamide; AVbCMF = doxorubicin, vinblastine, cyclophosphamide, methotrexate, 5-fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; CMFVA = cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, doxorubicin; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; FACV = 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine; HR = hazard ratio; CI = confidence interval

\* Includes pooled data from patients who received either AC alone for 4 cycles, or who were treated with AC for 4 cycles followed by 3 cycles of CMF.

† Patients received alternating cycles of AVb and CMF.

188

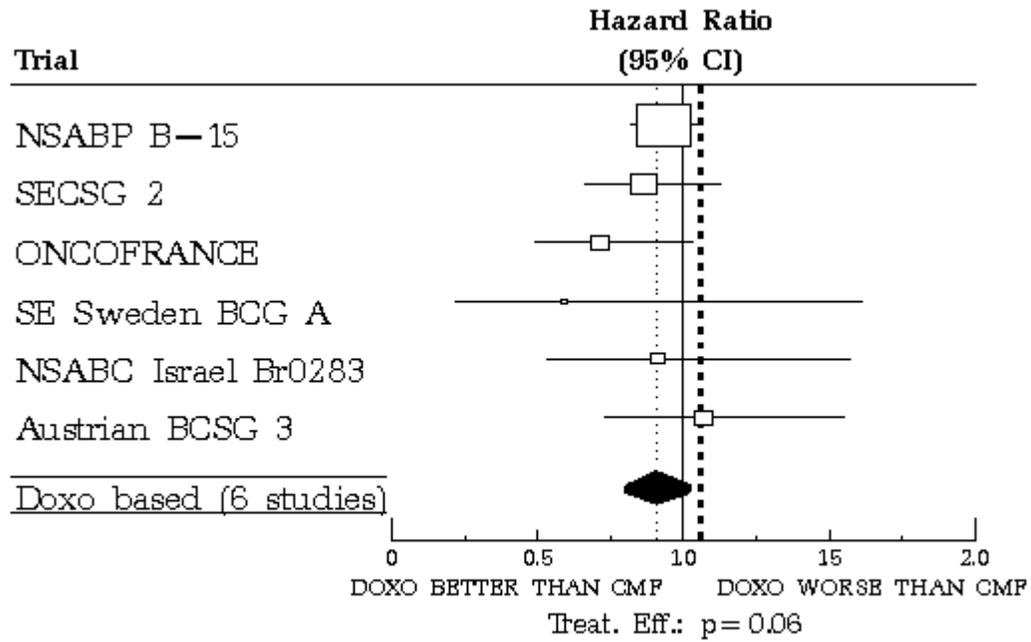
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191

**Figure 1. Meta-analysis of Disease-Free Survival**

192



--- Boundary of non-inferiority with CMF (1.06; 75% of CMF effect retained)

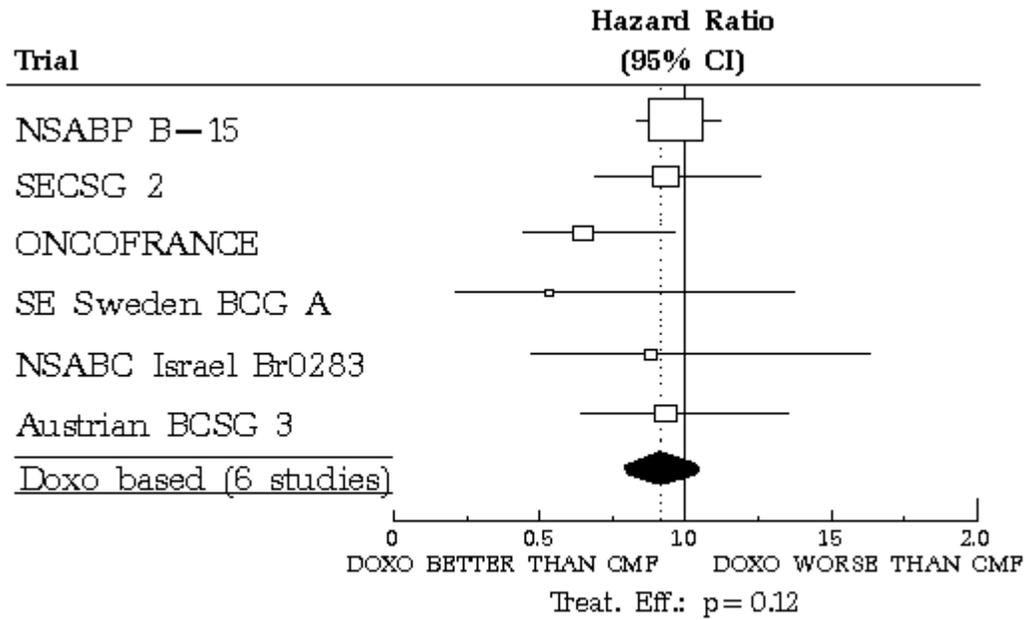
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195

196

**Figure 2. Meta-analysis of Overall Survival**



197

198 With respect to DFS, 2 of 6 studies (NSABP B-15 and ONCOFRANCE) met the non-  
 199 inferiority standard individually and with respect to OS, 1 study met the non-inferiority  
 200 margin individually (ONCOFRANCE). The largest of the 6 studies in the EBCTCG meta-  
 201 analysis, a randomized, open-label, multicenter trial (NSABP B-15) was conducted in  
 202 approximately 2300 women (80% premenopausal; 20% postmenopausal) with early breast  
 203 cancer involving axillary lymph nodes. In this trial, 6 cycles of conventional CMF was  
 204 compared to 4 cycles of doxorubicin and cyclophosphamide (AC) and 4 cycles of AC  
 205 followed by 3 cycles of CMF. No statistically significant differences in terms of DFS or OS  
 206 were observed. (See Table 1).

207

208

209

**INDICATIONS AND USAGE**

210 Doxorubicin has been used successfully to produce regression in disseminated neoplastic  
 211 conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms’  
 212 tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma,  
 213 transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin’s disease,

214 malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is  
215 the most responsive compared to other cell types.

216

217 Doxorubicin is also indicated for use as a component of adjuvant therapy in women with  
218 evidence of axillary lymph node involvement following resection of primary breast cancer.

219

220

## 221 **CONTRAINDICATIONS**

222 Patients should not be treated with doxorubicin if they have any of the following conditions:  
223 baseline neutrophil count  $<1500$  cells/mm<sup>3</sup>; severe hepatic impairment; recent myocardial  
224 infarction; severe myocardial insufficiency; severe arrhythmias; previous treatment with  
225 complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other  
226 anthracyclines and anthracenediones; or hypersensitivity to doxorubicin, any of its  
227 excipients, or other anthracyclines or anthracenediones. [See **WARNINGS and DOSAGE**  
228 **AND ADMINISTRATION**]

229

230

## 231 **WARNINGS**

### 232 **General**

233 Doxorubicin should be administered only under the supervision of qualified physicians  
234 experienced in the use of cytotoxic therapy. Patients should recover from acute toxicities of  
235 prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized  
236 infections) before beginning treatment with doxorubicin. Also, initial treatment with  
237 doxorubicin should be preceded by a careful baseline assessment of blood counts; serum  
238 levels of total bilirubin, AST, and creatinine; and cardiac function as measured by left  
239 ventricular ejection function (LVEF). Patients should be carefully monitored during  
240 treatment for possible clinical complications due to myelosuppression. Supportive care may  
241 be necessary for the treatment of severe neutropenia and severe infectious complications.  
242 Monitoring for potential cardiotoxicity is also important, especially with greater cumulative  
243 exposure to doxorubicin. Doxorubicin may potentiate the toxicity of other anticancer  
244 therapies (see **PRECAUTIONS, Drug Interactions**).

245

**246 Cardiac Function**

247 Cardiotoxicity is a known risk of anthracycline treatment. Anthracycline-induced  
248 cardiotoxicity may be manifested by early (or acute) or late (delayed) events.

249 Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or  
250 electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes.

251 Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia,  
252 bradycardia, as well as atrioventricular and bundle-branch block have also been reported.

253 These effects do not usually predict subsequent development of delayed cardiotoxicity, are  
254 rarely of clinical importance, and are generally not considered an indication for the  
255 suspension of doxorubicin treatment.

256

257 Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or  
258 within 2 to 3 months after treatment termination, but later events, several months to years  
259 after completion of treatment, have also been reported. Delayed cardiomyopathy is  
260 manifested by a reduction in LVEF and/or signs and symptoms of congestive heart failure  
261 (CHF) such as tachycardia, dyspnea, pulmonary edema, dependent edema, cardiomegaly and  
262 hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such  
263 as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe  
264 form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting  
265 toxicity of the drug.

266

267 The probability of developing impaired myocardial function, based on a combined index of  
268 signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1  
269 to 2% at a total cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin, 3 to 5% at a dose of 400  
270 mg/m<sup>2</sup>, 5 to 8% at a dose of 450 mg/m<sup>2</sup> and 6 to 20% at a dose of 500 mg/m<sup>2</sup> given in a  
271 schedule of a bolus injection once every 3 weeks. In a retrospective review, the probability  
272 of developing congestive heart failure was reported to be 5/168 (3%) at a cumulative dose of  
273 430 mg/m<sup>2</sup> of doxorubicin, 8/110 (7%) at 575 mg/m<sup>2</sup>, and 3/14 (21%) at 728 mg/m<sup>2</sup>. In a  
274 prospective study of doxorubicin in combination with cyclophosphamide, fluorouracil and/or  
275 vincristine in patients with breast cancer or small cell lung cancer, the probability of CHF at  
276 various cumulative doses of doxorubicin was 1.5% at 300 mg/m<sup>2</sup>, 4.9% at 400 mg/m<sup>2</sup>, 7.7%

277 at 450 mg/m<sup>2</sup> and 20.5% at 500 mg/m<sup>2</sup>. The risk of developing CHF increases rapidly with  
278 increasing total cumulative doses of doxorubicin in excess of 400 mg/m<sup>2</sup>.

279

280 Cardiotoxicity may occur at lower doses in patients with prior mediastinal/pericardial  
281 irradiation, concomitant use of other cardiotoxic drugs, doxorubicin exposure at an early age,  
282 and advanced age. Data also suggest that pre-existing heart disease is a cofactor for increased  
283 risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may occur at doses lower  
284 than the recommended cumulative dose of doxorubicin. Studies have suggested that  
285 concomitant administration of doxorubicin and calcium channel entry blockers may increase  
286 the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to the  
287 individual patient should also take into account previous or concomitant therapy with related  
288 compounds such as daunorubicin, idarubicin and mitoxantrone. Although not formally  
289 tested, it is probable that the toxicity of doxorubicin and other anthracyclines or  
290 anthracenediones is additive. Cardiomyopathy and/or congestive heart failure may be  
291 encountered several months or years after discontinuation of doxorubicin therapy.

292

293 The risk of acute manifestations of doxorubicin cardiotoxicity in pediatric patients may be as  
294 much or lower than in adults. Pediatric patients appear to be at particular risk for developing  
295 delayed cardiac toxicity in that doxorubicin- induced cardiomyopathy impairs myocardial  
296 growth as pediatric patients mature, subsequently leading to possible development of  
297 congestive heart failure during early adulthood. As many as 40% of pediatric patients may  
298 have subclinical cardiac dysfunction and 5 to 10% of pediatric patients may develop  
299 congestive heart failure on long term follow-up. This late cardiac toxicity may be related to  
300 the dose of doxorubicin. The longer the length of follow-up, the greater the increase in the  
301 detection rate. Treatment of doxorubicin-induced congestive heart failure includes the use of  
302 digitalis, diuretics, after load reducers such as angiotensin I converting enzyme (ACE)  
303 inhibitors, low salt diet, and bed rest. Such intervention may relieve symptoms and improve  
304 the functional status of the patient.

305

306 ***Monitoring Cardiac Function.*** The risk of serious cardiac impairment may be decreased  
307 through regular monitoring of LVEF during the course of treatment with prompt  
308 discontinuation of doxorubicin at the first sign of impaired function. The preferred method

309 for assessment of cardiac function is evaluation of LVEF measured by multi-gated  
310 radionuclide angiography (MUGA) or echocardiography (ECHO). An ECG may also be  
311 done. A baseline cardiac evaluation with a MUGA scan or an ECHO is recommended,  
312 especially in patients with risk factors for increased cardiac toxicity. Repeated MUGA or  
313 ECHO determinations of LVEF should be performed, particularly with higher, cumulative  
314 anthracycline doses. The technique used for assessment should be consistent through follow-  
315 up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the  
316 monitoring of cardiac function must be particularly strict and the risk-benefit of continuing  
317 treatment with doxorubicin in patients with impaired cardiac function must be carefully  
318 evaluated.

319

320 Endomyocardial biopsy is recognized as the most sensitive diagnostic tool to detect  
321 anthracycline-induced cardiomyopathy; however, this invasive examination is not practically  
322 performed on a routine basis. ECG changes such as dysrhythmias, a reduction of the QRS  
323 voltage, or a prolongation beyond normal limits of the systolic time interval may be  
324 indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific  
325 method for following anthracycline-related cardiotoxicity.

326

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

330

331 In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of  
332 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function.  
333 In pediatric patients, deterioration in cardiac function during or after the completion of  
334 therapy with doxorubicin is indicated by a drop in fractional shortening (FS) by an absolute  
335 value of  $\geq 10$  percentile units or below 29%, and a decline in LVEF of 10 percentile units or  
336 an LVEF below 55%. In general, if test results indicate deterioration in cardiac function  
337 associated with doxorubicin, the benefit of continued therapy should be carefully evaluated  
338 against the risk of producing irreversible cardiac damage. Acute life-threatening arrhythmias  
339 have been reported to occur during or within a few hours after doxorubicin administration.

340

**341 Hematologic Toxicity**

342 As with other cytotoxic agents, doxorubicin may produce myelosuppression.  
343 Myelosuppression requires careful monitoring. Total and differential WBC, red blood cell  
344 (RBC), and platelet counts should be assessed before and during each cycle of therapy with  
345 doxorubicin. A dose-dependent, reversible leukopenia and/or granulocytopenia  
346 (neutropenia) are the predominant manifestations of doxorubicin hematologic toxicity and is  
347 the most common acute dose-limiting toxicity of this drug. With the recommended dose  
348 schedule, leukopenia is usually transient, reaching its nadir 10 to 14 days after treatment with  
349 recovery usually occurring by the 21st day. Thrombocytopenia and anemia may also occur.  
350 Clinical consequences of severe myelosuppression include fever, infections,  
351 sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

352

**353 Secondary Leukemia**

354 The occurrence of secondary AML or MDS has been reported most commonly in patients  
355 treated with chemotherapy regimens containing anthracyclines (including doxorubicin) and  
356 DNA-damaging antineoplastic agents, in combination with radiotherapy, when patients have  
357 been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been  
358 escalated. Such cases generally have a 1-3 year latency period. The rate of developing  
359 secondary AML or MDS has been estimated in an analysis of 8563 patients with early breast  
360 cancer treated in 6 studies conducted by the National Surgical Adjuvant Breast and Bowel  
361 Project (NSABP), including NSABP B-15. Patients in these studies received standard doses  
362 of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant  
363 chemotherapy and were followed for 61,810 patient years. Among 4483 such patients who  
364 received conventional doses of AC, 11 cases of AML or MDS were identified, for an  
365 incidence of 0.32 cases per 1000 patient years (95% CI 0.16-0.57) and a cumulative  
366 incidence at 5 years of 0.21% (95% CI 0.11-0.41%). In another analysis of 1474 patients  
367 with breast cancer who received adjuvant treatment with doxorubicin-containing regimens in  
368 clinical trials conducted at University of Texas M.D. Anderson Cancer Center, the incidence  
369 was estimated at 1.5% at 10 years. In both experiences, patients who received regimens with  
370 higher cyclophosphamide dosages, who received radiotherapy, or who were aged 50 or older  
371 had an increased risk of secondary AML or MDS.

372

373 Pediatric patients are also at risk of developing secondary AML.

374

### 375 **Effects at Site of Injection**

376 Phleboscrosis may result from an injection into a small vessel or from repeated injections  
377 into the same vein. Following the recommended administration procedures may minimize the  
378 risk of phlebitis/thrombophlebitis at the injection site (see DOSAGE AND  
379 ADMINISTRATION, Instruction for Use/Handling).

380

### 381 **Extravasation**

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

387

### 388 **Hepatic Impairment**

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

394

### 395 **Pregnancy Category D**

396

397 Doxorubicin can cause fetal harm when administered to a pregnant woman. Doxorubicin was  
398 teratogenic and embryotoxic at doses of 0.8 mg/kg/day (about 1/13 the recommended human  
399 dose on a body surface area basis) when administered during the period of organogenesis in  
400 rats. Teratogenicity and embryotoxicity were also seen using discrete periods of treatment.  
401 The most susceptible was the 6- to 9-day gestation period at doses of 1.25 mg/kg/day and  
402 greater. Characteristic malformations included esophageal and intestinal atresia, tracheo-  
403 esophageal fistula, hypoplasia of the urinary bladder and cardiovascular anomalies.

404 Doxorubicin was embryotoxic (increase in embryofetal deaths) and abortifacient at 0.4

405 mg/kg/day (about 1/14 the recommended human dose on a body surface area basis) in rabbits  
406 when administered during the period of organogenesis.

407  
408 There are no adequate and well-controlled studies in pregnant women. If doxorubicin is to  
409 be used during pregnancy, or if the patient becomes pregnant during therapy, the patient  
410 should be apprised of the potential hazard to the fetus. Women of childbearing age should be  
411 advised to avoid becoming pregnant.

412

413

## 414 **PRECAUTIONS**

### 415 **General**

416 Doxorubicin is not an anti-microbial agent. Doxorubicin is emetogenic. Antiemetics may  
417 reduce nausea and vomiting; prophylactic use of antiemetics should be considered before  
418 administration of doxorubicin, particularly when given in conjunction with other emetogenic  
419 drugs.

420

### 421 **Information for Patients**

422 Patients should be informed of the expected adverse effects of doxorubicin, including  
423 gastrointestinal symptoms (nausea, vomiting, diarrhea, and stomatitis) and potential  
424 neutropenic complications. Patients should consult their physician if vomiting, dehydration,  
425 fever, evidence of infection, symptoms of CHF, or injection-site pain occurs  
426 following therapy with doxorubicin. Patients should be informed that they will almost  
427 certainly develop alopecia. Patients should be advised that their urine may appear red for 1  
428 to 2 days after administration of doxorubicin and that they should not be alarmed. Patients  
429 should understand that there is a risk of irreversible myocardial damage associated with  
430 treatment with doxorubicin, as well as a risk of treatment-related leukemia. Because  
431 doxorubicin may induce chromosomal damage in sperm, men undergoing treatment with  
432 doxorubicin should use effective contraceptive methods. Women treated with doxorubicin  
433 may develop irreversible amenorrhea, or premature menopause.

434

435 **Drug Interactions**

436 Doxorubicin is extensively metabolized by the liver. Changes in hepatic function induced by  
437 concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic  
438 efficacy, and/or toxicity. Toxicities associated with doxorubicin, especially hematologic and  
439 gastrointestinal events, may be increased when doxorubicin is used in combination with other  
440 cytotoxic drugs.

441 **Paclitaxel:** There have been a number of reports in the literature that describe an increase in  
442 cardiotoxicity when doxorubicin is co-administered with paclitaxel. Two published studies  
443 report that initial administration of paclitaxel infused over 24 hours followed by doxorubicin  
444 administered over 48 hours resulted in a significant decrease in doxorubicin clearance with  
445 more profound neutropenic and stomatitis episodes than the reverse sequence of  
446 administration.

447 **Progesterone:** In a published study, progesterone was given intravenously to patients with  
448 advanced malignancies (ECOG PS<2) at high doses (up to 10 g over 24 hours)  
449 concomitantly with a fixed doxorubicin dose (60 mg/m<sup>2</sup>) via bolus injection. Enhanced  
450 doxorubicin-induced neutropenia and thrombocytopenia were observed.

451 **Verapamil:** A study of the effects of verapamil on the acute toxicity of doxorubicin in mice  
452 revealed higher initial peak concentrations of doxorubicin in the heart with a higher  
453 incidence and severity of degenerative changes in cardiac tissue resulting in a shorter  
454 survival.

455 **Cyclosporine:** The addition of cyclosporine to doxorubicin may result in increases in AUC  
456 for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug  
457 and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding  
458 cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity  
459 than doxorubicin alone. Coma and/or seizures have also been described.

460 **Dexrazoxane:** In a clinical study of women with metastatic breast cancer, the concurrent  
461 use of the cardioprotectant, dexrazoxane, with the initiation of a regimen of fluorouracil,  
462 doxorubicin, and cyclophosphamide (FAC) was associated with a lower tumor response rate.  
463 Later initiation of dexrazoxane (after administration of a cumulative doxorubicin dose of 300  
464 mg/m<sup>2</sup> of doxorubicin had been given as a component of FAC) was not associated with a  
465 reduction in chemotherapy activity. Dexrazoxane is only indicated for use in women with

466 metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m<sup>2</sup> and  
467 are continuing with doxorubicin therapy.

468 **Cytarabine:** Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools  
469 and severe and sometimes fatal infections have been associated with a combination of  
470 doxorubicin given by intravenous push daily for 3 days and cytarabine given by continuous  
471 infusion daily for 7 or more days.

472 **Cyclophosphamide:** The addition of cyclophosphamide to doxorubicin treatment does not  
473 affect exposure to doxorubicin, but may result in an increase in exposure to doxorubicinol, a  
474 metabolite. Doxorubicinol only has 5% of the cytotoxic activity of doxorubicin. Concurrent  
475 treatment with doxorubicin has been reported to exacerbate cyclophosphamide-induced  
476 hemorrhagic cystitis. Acute myeloid leukemia has been reported as a second malignancy  
477 after treatment with doxorubicin and cyclophosphamide.

478 **Literature reports have also described the following drug interactions:** Phenobarbital  
479 increases the elimination of doxorubicin; phenytoin levels may be decreased by doxorubicin;  
480 streptozocin (Zanosar®) may inhibit hepatic metabolism of doxorubicin; saquinavir in  
481 combination with cyclophosphamide, doxorubicin, and etoposide increased mucosal toxicity  
482 in patients with HIV-associated non-Hodgkin's lymphoma; and administration of live  
483 vaccines to immunosuppressed patients including those undergoing cytotoxic chemotherapy  
484 may be hazardous.

485

#### 486 **Laboratory Tests**

487 Initial treatment with doxorubicin requires observation of the patient and periodic monitoring  
488 of complete blood counts, hepatic function tests, and left ventricular ejection fraction. (See  
489 WARNINGS). Abnormalities of hepatic function tests may occur. Like other cytotoxic  
490 drugs, doxorubicin may induce "tumor lysis syndrome" and hyperuricemia in patients with  
491 rapidly growing tumors. . Blood uric acid levels, potassium, calcium, phosphate, and  
492 creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and  
493 prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications  
494 of tumor-lysis syndrome.

495

496 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

497 Carcinogenicity studies have not been conducted with doxorubicin. Secondary acute  
498 myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have been reported in  
499 patients treated with doxorubicin-containing combination chemotherapy regimens (see  
500 WARNINGS). Pediatric patients treated with doxorubicin or other topoisomerase II  
501 inhibitors are at risk for developing acute myelogenous leukemia and other neoplasms.  
502 Doxorubicin was mutagenic in the in vitro Ames assay, and clastogenic in multiple in vitro  
503 assays (CHO cell, V79 hamster cell, human lymphoblast, and SCE assays) and the in vivo  
504 mouse micronucleus assay.

505

506 Doxorubicin decreased fertility in female rats at the doses of 0.05 and 0.2 mg/kg/day (about  
507 1/200 and 1/50 the recommended human dose on a body surface area basis) when  
508 administered from 14 days before mating through late gestation period. A single i.v. dose of  
509 doxorubicin at 0.1 mg/kg (about 1/100 the recommended human dose on a body surface area  
510 basis) was toxic to male reproductive organs producing testicular atrophy and oligospermia  
511 in rats. Doxorubicin is mutagenic as it induced DNA damage in rabbit spermatozoa and  
512 dominant lethal mutations in mice. Therefore, doxorubicin may potentially induce  
513 chromosomal damage in human spermatozoa. Oligospermia or azoospermia were evidenced  
514 in men treated with doxorubicin, mainly in combination therapies. Men undergoing  
515 doxorubicin treatment should use effective contraceptive methods.

516

517 Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular  
518 atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia. Doxorubicin is  
519 mutagenic as it induces DNA damage in rabbit spermatozoa and dominant lethal mutations in  
520 mice. Therefore, doxorubicin can potentially induce chromosomal damage in human  
521 spermatozoa. Oligospermia or azoospermia were evidenced in men treated with doxorubicin,  
522 mainly in combination therapies. This effect may be permanent. However, sperm counts  
523 have been reported to return to normal levels in some instances. This may occur several  
524 years after the end of the therapy. Men undergoing doxorubicin treatment should use  
525 effective contraceptive methods.

526

527 In women, doxorubicin may cause infertility during the time of drug administration.  
528 Doxorubicin may cause amenorrhea. Ovulation and menstruation may return after  
529 termination of therapy, although premature menopause can occur. Recovery of menses is  
530 related to age at treatment.

531

532 Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have  
533 been reported in patients treated with anthracycline-containing adjuvant combination  
534 chemotherapy regimens (see WARNINGS, Hematologic).

535

### 536 **Pregnancy Category D**

537 (See WARNINGS.)

538

### 539 **Nursing Mothers**

540 Doxorubicin and its major metabolite, doxorubicinol have been detected in the milk of at  
541 least one lactating patient (see CLINICAL PHARMACOLOGY, Pharmacokinetics).  
542 Because of the potential for serious adverse reactions in nursing infants from doxorubicin,  
543 mothers should be advised to discontinue nursing during doxorubicin therapy.

544

### 545 **Pediatric Use**

546 Pediatric patients are at increased risk for developing delayed cardiotoxicity. Follow-up  
547 cardiac evaluations are recommended periodically to monitor for this delayed cardiotoxicity  
548 (see WARNINGS). Doxorubicin, as a component of intensive chemotherapy regimens  
549 administered to pediatric patients, may contribute to prepubertal growth failure. It may also  
550 contribute to gonadal impairment, which is usually temporary. Pediatric patients treated with  
551 doxorubicin or other topoisomerase II inhibitors are at a risk for developing acute  
552 myelogenous leukemia and other neoplasms. Pediatric patients receiving concomitant  
553 doxorubicin and actinomycin-D have manifested acute “recall” pneumonitis at variable  
554 times after local radiation therapy.

555

### 556 **Geriatric Use**

557 An estimated 4600 patients who were 65 and over were included in the reported clinical  
558 experience of doxorubicin use for various indications. No overall differences in safety and

559 effectiveness were observed between these patients and younger patients, but greater  
560 sensitivity of some older individuals cannot be ruled out. The decision to use doxorubicin in  
561 the treatment of older patients should be based upon a consideration of overall performance  
562 status and concurrent illnesses, in addition to age of the individual patient.

563

564

## 565 **ADVERSE REACTIONS**

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

568 *Cardiotoxicity* - (See WARNINGS.)

569 *Cutaneous* - Reversible complete alopecia occurs in most cases. Hyperpigmentation of  
570 nailbeds and dermal creases, primarily in pediatric patients, and onycholysis have been  
571 reported in a few cases. Radiation recall reaction has occurred with doxorubicin  
572 administration. Rash, itching, or photosensitivity may occur.

573 *Gastrointestinal* - Acute nausea and vomiting occurs frequently and may be severe. This  
574 may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur  
575 within 5 to 10 of beginning therapy, and most patients recover from this adverse event within  
576 another 5 to 10 days. The effect may be severe leading to ulceration and represents a site of  
577 origin for severe infections. The dosage regimen consisting of administration of doxorubicin  
578 on three successive days results in greater incidence and severity of mucositis. Ulceration  
579 and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe  
580 infections which can be fatal. This reaction has been reported in patients with acute non-  
581 lymphocytic leukemia treated with a 3-day course of doxorubicin combined with cytarabine.  
582 Anorexia, abdominal pain, dehydration, diarrhea, and hyperpigmentation of the oral mucosa  
583 have been occasionally reported.

584 *Hematologic* - (See WARNINGS)

585 *Hypersensitivity* - Fever, chills and urticaria have been reported occasionally. Anaphylaxis  
586 may occur. A case of apparent cross sensitivity to lincomycin has been reported.

587 *Neurological* - Peripheral neurotoxicity in the form of local-regional sensory and/or motor  
588 disturbances have been reported in patients treated intra-arterially with doxorubicin, mostly  
589 in combination with cisplatin. Animal studies have demonstrated seizures and coma in  
590 rodents and dogs treated with intra-carotid doxorubicin. Seizures and coma have been  
591 reported in patients treated with doxorubicin in combination with cisplatin or vincristine.

592 *Ocular* - Conjunctivitis, keratitis, and lacrimation occur rarely.

593 *Other* - Malaise/asthenia have been reported.

594

595 *Adverse Reactions in Patients with Early Breast Cancer Receiving Doxorubicin-Containing*

596 *Adjuvant Therapy*: Safety data were collected from approximately 2300 women who

597 participated in a randomized, open-label trial (NSABP B-15) evaluating the use of AC versus

598 CMF in the treatment of early breast cancer involving axillary lymph nodes. In the safety

599 analysis, the follow-up data from all patients receiving AC were combined (N=1492

600 evaluable patients) and compared with data from patients receiving conventional CMF (i.e.,

601 oral cyclophosphamide; N=739 evaluable patients). The most relevant adverse events

602 reported in this study are provided in Table 2.

603

**Table 2. Relevant Adverse Events in Patients with Early Breast Cancer Involving Axillary Lymph Nodes**

	AC*	Conventional CMF
	N=1492	N=739
Treatment administration		
Mean number of cycles	3.8	5.5
Total cycles	5676	4068
Adverse events, % of patients		
Leukopenia		
Grade 3 (1,000-1,999 /mm <sup>3</sup> )	3.4	9.4
Grade 4 (<1000 /mm <sup>3</sup> )	0.3	0.3
Thrombocytopenia		
Grade 3 (25,000-49,999 /mm <sup>3</sup> )	0	0.3
Grade 4 (<25,000 /mm <sup>3</sup> )	0.1	0
Shock, sepsis	1.5	0.9
Systemic infection	2.4	1.2
Nausea and vomiting		
Nausea only	15.5	42.8
Vomiting ≤12 hours	34.4	25.2
Vomiting >12 hours	36.8	12.0
Intractable	4.7	1.6
Alopecia	92.4	71.4
Partial	22.9	56.3
Complete	69.5	15.1
Weight loss		
5-10%	6.2	5.7
>10%	2.4	2.8
Weight gain		
5-10%	10.6	27.9
>10%	3.8	14.3
Cardiac function		
Asymptomatic	0.2	0.1
Transient	0.1	0
Symptomatic	0.1	0
Treatment-related death	0	0

\* Includes pooled data from patients who received either AC alone for 4 cycles, or who were treated with AC for 4 cycles followed by 3 cycles of CMF

604

605

**606 OVERDOSAGE**

607 Acute overdosage with doxorubicin enhances the toxic effect of mucositis, leukopenia and  
608 thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely  
609 myelosuppressed patient with hospitalization, antimicrobials, platelet transfusions and  
610 symptomatic treatment of mucositis. Use of hemopoietic growth factor (G-CSF, GM-CSF)  
611 may be considered. The 150 mg doxorubicin hydrochloride for injection and the 75 mL and  
612 100 mL (2 mg/mL) doxorubicin hydrochloride injection vials are packaged as multiple dose

613 vials and caution should be exercised to prevent inadvertent overdosage. Cumulative dosage  
614 with doxorubicin increases the risk of cardiomyopathy and resultant congestive heart failure  
615 (see WARNINGS). Treatment consists of vigorous management of congestive heart failure  
616 with digitalis preparations, diuretics, and after-load reducers such as ACE inhibitors.

617

618

## 619 **DOSAGE AND ADMINISTRATION**

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

631

632 The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m<sup>2</sup> as a  
633 single intravenous injection administered at 21-day intervals. The lower dosage should be  
634 given to patients with inadequate marrow reserves due to old age, or prior therapy, or  
635 neoplastic marrow infiltration.

636

637 Doxorubicin has been used concurrently with other approved chemotherapeutic agents.  
638 Evidence is available that in some types of neoplastic disease combination chemotherapy is  
639 superior to single agents. The benefits and risks of such therapy continue to be elucidated.  
640 When used in combination with other chemotherapy drugs, the most commonly used dosage  
641 of doxorubicin is 40 to 60 mg/m<sup>2</sup> given as a single intravenous injection every 21 to 28 days.

642

643 In a large randomized study (NSABP B-15) of patients with early breast cancer involving  
644 axillary lymph nodes (see CLINICAL PHARMACOLOGY, Clinical Studies and ADVERSE

645 REACTIONS, Adverse Reactions in Patients with Early Breast Cancer Receiving  
 646 Doxorubicin-Containing Adjuvant Therapy), the combination dosage regimen of AC  
 647 (doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup>) was administered intravenously  
 648 on day 1 of each 21-day treatment cycle. Four cycles of treatment were administered.

649

### 650 **Dose Modifications**

651 Patients in the NSABP B-15 study could have dose modifications of AC to 75% of the  
 652 starting doses for neutropenic fever/infection. When necessary, the next cycle of treatment  
 653 cycle was delayed until the absolute neutrophil count (ANC) was  $\geq 1000$  cells/mm<sup>3</sup> and the  
 654 platelet count was  $\geq 100,000$  cells/mm<sup>3</sup> and nonhematologic toxicities had resolved.

655

656 Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

Plasma bilirubin concentration (mg/dL)	Dosage reduction (%)
1.2 - 3.0	50
3.1 - 5.0	75

657

658

### 659 **Reconstitution Directions**

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

670

671 Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that  
 672 these drugs are incompatible to the extent that a precipitate may form. Contact with alkaline  
 673 solutions should be avoided since this can lead to hydrolysis of doxorubicin. Until specific

674 compatibility data are available, it is not recommended that doxorubicin be mixed with other  
675 drugs.

676

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

679

### 680 **Handling and Disposal**

681 Procedures for proper handling and disposal of anti-cancer drugs should be considered.

682 Several guidelines on this subject have been published.<sup>1-8</sup> There is no general agreement that  
683 all the procedures recommended in the guidelines are necessary or appropriate. However,  
684 given the toxic nature of this substance, the following protective recommendations are provided:

685

- 686 • Personnel should be trained in good technique for reconstitution and handling.
- 687 • Pregnant staff should be excluded from working with this drug.
- 688 • Personnel handling doxorubicin should wear protective clothing: goggles, gowns and  
689 disposable gloves and masks.
- 690 • A designated area should be defined for reconstitution (preferably under a laminar flow  
691 system). The work surface should be protected by disposable, plastic-backed, absorbent  
692 paper.
- 693 • All items used for reconstitution, administration or cleaning, including gloves, should be  
694 placed in high-risk waste-disposal bags for high-temperature incineration.
- 695 • Spillage or leakage should be treated with dilute sodium hypochlorite (1% available  
696 chlorine) solution, preferably by soaking, and then water.
- 697 • All cleaning materials should be disposed of as indicated previously.
- 698 • In case of skin contact thoroughly wash the affected area with soap and water or  
699 sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- 700 • In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s)  
701 with copious amounts of water for at least 15 minutes. Then seek medical evaluation  
702 by a physician.
- 703 • Always wash hands after removing gloves.

704

705 Caregivers of pediatric patients receiving doxorubicin should be counseled to take  
706 precautions (such as wearing latex gloves) to prevent contact with the patient's urine and  
707 other body fluids for at least 5 days after each treatment.

708

709

## 710 **HOW SUPPLIED**

711

712 **Doxorubicin Hydrochloride for Injection, USP**, a sterile red-orange lyophilized powder for  
713 intravenous use only, is available in 10, 20 and 50 mg single dose vials and a 150 mg  
714 multidose vial.

715 Each 10 mg single dose vial contains 10 mg of doxorubicin HCl, USP, 50 mg of lactose, NF  
716 (hydrous) and 1 mg of methylparaben, NF (added to enhance dissolution).

717 Each 20 mg single dose vial contains 20 mg of doxorubicin HCl, USP, 100 mg of lactose, NF  
718 (hydrous) and 2 mg of methylparaben, NF (added to enhance dissolution).

719 Each 50 mg single dose vial contains 50 mg of doxorubicin HCl, USP, 250 mg of lactose, NF  
720 (hydrous) and 5 mg of methylparaben, NF (added to enhance dissolution).

721 Each 150 mg multidose vial contains 150 mg of doxorubicin HCl, USP, 750 mg of lactose,  
722 NF (hydrous) and 15 mg of methylparaben, NF (added to enhance dissolution).

723 **Doxorubicin Hydrochloride for Injection, USP** is available as:

724 Sterile single use only:

725 NDC 0013-1086-91 10 mg single dose vial, 10 vial packs

726 NDC 0013-1096-91 20 mg single dose vial, 10 vial packs

727 NDC 0013-1106-79 50 mg single dose vial, single packs

728 Multidose vial:

729 NDC 0013-1116-83 150 mg multidose vial, single packs

730

731 Store at controlled room temperature, 15° to 30°C (59° to 86°F). Protect from light. Retain in  
732 carton until time of use. Discard unused portion.

733

## 734 **Reconstituted Solution Stability**

735 After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The  
736 reconstituted solution is stable for 7 days at room temperature and under normal room light

737 (100 foot-candles) and 15 days under refrigeration (2° to 8°C). It should be protected from  
738 exposure to sunlight. Discard any unused solution from the 10 mg, 20 mg and 50 mg single  
739 dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended  
740 storage times should be discarded.

741

742 **Doxorubicin Hydrochloride Injection, USP**, is a sterile parenteral, isotonic, available in 5  
743 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg), and 37.5 mL (75 mg) single dose vials and a  
744 100 mL (200 mg) multidose vial. Each mL contains doxorubicin HCl and the following  
745 inactive ingredients: sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is  
746 used to adjust the pH to a target pH of 3.0.

747

748 **Doxorubicin Hydrochloride Injection, USP** is available as:

749 SINGLE DOSE GLASS VIALS:

750 NDC 0013-1136-91 10 mg vial, 2 mg/mL, 5 mL, 10 vial packs

751 NDC 0013-1146-91 20 mg vial, 2 mg/mL, 10 mL, 10 vial packs

752 NDC 0013-1156-79 50 mg vial, 2 mg/mL, 25 mL, single vial packs

753 NDC 0013-1176-87 75 mg vial, 2 mg/mL, 37.5 mL, single vial packs

754 MULTIDOSE VIALS, in Cytosafe™ vial packs:

755 NDC 0013-1286-83 150 mg, 2 mg/mL, 75 mL

756 NDC 0013-1266-83 200 mg, 2 mg/mL, 100 mL

757

758 Store refrigerated, 2° to 8°C (36° to 46°F). Protect from light. Retain in carton until contents  
759 are used. Contains no preservative. Discard unused portion.

760

761

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