

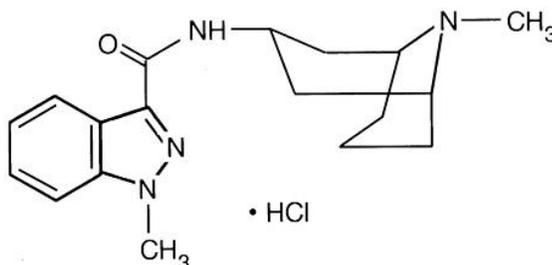


**(granisetron hydrochloride)**  
**INJECTION**

**Rx only**

**DESCRIPTION**

KYTRIL (granisetron hydrochloride) Injection is an antiemetic and anti-nauseant agent. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is  $C_{18}H_{24}N_4O \cdot HCl$ , while its chemical structure is:



granisetron hydrochloride

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C. KYTRIL Injection is a clear, colorless, sterile, nonpyrogenic, aqueous solution for intravenous administration.

KYTRIL 1 mg/1 mL is available in 1 mL single-use and 4 mL multi-use vials. KYTRIL 0.1 mg/1 mL is available in a 1 mL single-use vial.

1 mg/1 mL: Each 1 mL contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg; sodium chloride, 9 mg; citric acid, 2 mg; and benzyl alcohol, 10 mg, as a preservative. The solution's pH ranges from 4.0 to 6.0.

0.1 mg/1 mL: Each 1 mL contains 0.112 mg granisetron hydrochloride equivalent to granisetron, 0.1 mg; sodium chloride, 9 mg; citric acid, 2 mg. Contains no preservative. The solution's pH ranges from 4.0 to 6.0.

**CLINICAL PHARMACOLOGY**

Granisetron is a selective 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT<sub>1</sub>; 5-HT<sub>1A</sub>; 5-HT<sub>1B/C</sub>; 5-HT<sub>2</sub>; for alpha<sub>1</sub>-, alpha<sub>2</sub>- or beta-adrenoreceptors; for dopamine-D<sub>2</sub>; or for histamine-H<sub>1</sub>; benzodiazepine; picrotoxin or opioid receptors.

29 Serotonin receptors of the 5-HT<sub>3</sub> type are located peripherally on vagal nerve terminals  
30 and centrally in the chemoreceptor trigger zone of the area postrema. During  
31 chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin,  
32 which stimulates 5-HT<sub>3</sub> receptors. This evokes vagal afferent discharge and may induce  
33 vomiting. Animal studies demonstrate that, in binding to 5-HT<sub>3</sub> receptors, granisetron  
34 blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as  
35 cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting  
36 due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

37 In most human studies, granisetron has had little effect on blood pressure, heart rate or  
38 ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has  
39 been found in other studies.

40 KYTRIL Injection exhibited no effect on oro-cecal transit time in normal volunteers  
41 given a single intravenous infusion of 50 mcg/kg or 200 mcg/kg. Single and multiple oral  
42 doses slowed colonic transit in normal volunteers.

### 43 **Pharmacokinetics**

#### 44 **Chemotherapy-Induced Nausea and Vomiting**

45 In adult cancer patients undergoing chemotherapy and in volunteers, mean  
46 pharmacokinetic data obtained from an infusion of a single 40 mcg/kg dose of KYTRIL  
47 Injection are shown in Table 1.

48 **Table 1**                    **Pharmacokinetic Parameters in Adult Cancer Patients**  
49                                    **Undergoing Chemotherapy and in Volunteers, Following a**  
50                                    **Single Intravenous 40 mcg/kg Dose of KYTRIL Injection**

	<b>Peak Plasma Concentration (ng/mL)</b>	<b>Terminal Phase Plasma Half-Life (h)</b>	<b>Total Clearance (L/h/kg)</b>	<b>Volume of Distribution (L/kg)</b>
<b>Cancer Patients</b>				
Mean	63.8*	8.95*	0.38*	3.07*
Range	18.0 to 176	0.90 to 31.1	0.14 to 1.54	0.85 to 10.4
<b>Volunteers</b>				
21 to 42 years				
Mean	64.3 <sup>†</sup>	4.91 <sup>†</sup>	0.79 <sup>†</sup>	3.04 <sup>†</sup>
Range	11.2 to 182	0.88 to 15.2	0.20 to 2.56	1.68 to 6.13
65 to 81 years				
Mean	57.0 <sup>†</sup>	7.69 <sup>†</sup>	0.44 <sup>†</sup>	3.97 <sup>†</sup>
Range	14.6 to 153	2.65 to 17.7	0.17 to 1.06	1.75 to 7.01

51 \*5-minute infusion.

52 <sup>†</sup>3-minute infusion.

### 53 **Distribution**

54 Plasma protein binding is approximately 65% and granisetron distributes freely between  
55 plasma and red blood cells.

56 **Metabolism**

57 Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed  
58 by conjugation. In vitro liver microsomal studies show that granisetron's major route of  
59 metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the  
60 cytochrome P-450 3A subfamily. Animal studies suggest that some of the metabolites  
61 may also have 5-HT<sub>3</sub> receptor antagonist activity.

62 **Elimination**

63 Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately  
64 12% of the administered dose is eliminated unchanged in the urine in 48 hours. The  
65 remainder of the dose is excreted as metabolites, 49% in the urine, and 34% in the feces.

66 **Subpopulations**

67 **Gender**

68 There was high inter- and intra-subject variability noted in these studies. No difference in  
69 mean AUC was found between males and females, although males had a higher C<sub>max</sub>  
70 generally.

71 **Elderly**

72 The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years),  
73 given a single 40 mcg/kg intravenous dose of KYTRIL Injection, were generally similar  
74 to those in younger healthy volunteers; mean values were lower for clearance and longer  
75 for half-life in the elderly patients (see Table 1).

76 **Pediatric Patients**

77 A pharmacokinetic study in pediatric cancer patients (2 to 16 years of age), given a single  
78 40 mcg/kg intravenous dose of KYTRIL Injection, showed that volume of distribution  
79 and total clearance increased with age. No relationship with age was observed for peak  
80 plasma concentration or terminal phase plasma half-life. When volume of distribution  
81 and total clearance are adjusted for body weight, the pharmacokinetics of granisetron are  
82 similar in pediatric and adult cancer patients.

83 **Renal Failure Patients**

84 Total clearance of granisetron was not affected in patients with severe renal failure who  
85 received a single 40 mcg/kg intravenous dose of KYTRIL Injection.

86 **Hepatically Impaired Patients**

87 A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver  
88 involvement showed that total clearance was approximately halved compared to patients  
89 without hepatic impairment. Given the wide variability in pharmacokinetic parameters  
90 noted in patients and the good tolerance of doses well above the recommended 10 mcg/kg  
91 dose, dosage adjustment in patients with possible hepatic functional impairment is not  
92 necessary.

93 **Postoperative Nausea and Vomiting**

94 In adult patients (age range, 18 to 64 years) recovering from elective surgery and  
95 receiving general balanced anesthesia, mean pharmacokinetic data obtained from a single  
96 1 mg dose of KYTRIL Injection administered intravenously over 30 seconds are shown  
97 in **Table 2**.

98 **Table 2**                   **Pharmacokinetic Parameters in 16 Adult Surgical Patients**  
99 **Following a Single Intravenous 1 mg Dose of KYTRIL**  
100 **Injection**

	<b>Terminal Phase Plasma Half-Life (h)</b>	<b>Total Clearance (L/h/kg)</b>	<b>Volume of Distribution (L/kg)</b>
Mean	8.63	0.28	2.42
Range	1.77 to 17.73	0.07 to 0.71	0.71 to 4.13

101

102 The pharmacokinetics of granisetron in patients undergoing surgery were similar to those  
103 seen in cancer patients undergoing chemotherapy.

104 **CLINICAL TRIALS**

105 **Chemotherapy-Induced Nausea and Vomiting**

106 *Single-Day Chemotherapy*

107 *Cisplatin-Based Chemotherapy*

108 In a double-blind, placebo-controlled study in 28 cancer patients, KYTRIL Injection,  
109 administered as a single intravenous infusion of 40 mcg/kg, was significantly more  
110 effective than placebo in preventing nausea and vomiting induced by cisplatin  
111 chemotherapy (see Table 3).

112 **Table 3**                   **Prevention of Chemotherapy-Induced Nausea and Vomiting**  
113 **— Single-Day Cisplatin Therapy<sup>1</sup>**

	<b>KYTRIL Injection</b>	<b>Placebo</b>	<b>P-Value</b>
Number of Patients	14	14	
Response Over 24 Hours			
Complete Response <sup>2</sup>	93%	7%	<0.001
No Vomiting	93%	14%	<0.001
No More Than Mild Nausea	93%	7%	<0.001

114 <sup>1</sup> Cisplatin administration began within 10 minutes of KYTRIL Injection infusion and  
115 continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m<sup>2</sup> in the KYTRIL  
116 Injection group and 80 mg/m<sup>2</sup> in the placebo group.

117 <sup>2</sup> No vomiting and no moderate or severe nausea.

118 KYTRIL Injection was also evaluated in a randomized dose response study of cancer  
119 patients receiving cisplatin ≥75 mg/m<sup>2</sup>. Additional chemotherapeutic agents included:

120 anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydrazine,  
121 nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs, and vinca  
122 alkaloids. KYTRIL Injection doses of 10 and 40 mcg/kg were superior to 2 mcg/kg in  
123 preventing cisplatin-induced nausea and vomiting, but 40 mcg/kg was not significantly  
124 superior to 10 mcg/kg (see Table 4).

125 **Table 4**                    **Prevention of Chemotherapy-Induced Nausea and Vomiting**  
126                                    **— Single-Day High-Dose Cisplatin Therapy<sup>1</sup>**

	KYTRIL Injection (mcg/kg)			P-Value (vs. 2 mcg/kg)	
	2	10	40	10	40
Number of Patients	52	52	53		
Response Over 24 Hours					
Complete Response <sup>2</sup>	31%	62%	68%	<0.002	<0.001
No Vomiting	38%	65%	74%	<0.001	<0.001
No More Than Mild Nausea	58%	75%	79%	NS	0.007

127 <sup>1</sup> Cisplatin administration began within 10 minutes of KYTRIL Injection infusion and  
128 continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m<sup>2</sup>.

129 <sup>2</sup> No vomiting and no moderate or severe nausea.

130 KYTRIL Injection was also evaluated in a double-blind, randomized dose response study  
131 of 353 patients stratified for high (≥80 to 120 mg/m<sup>2</sup>) or low (50 to 79 mg/m<sup>2</sup>) cisplatin  
132 dose. Response rates of patients for both cisplatin strata are given in Table 5.

133 **Table 5**                    **Prevention of Chemotherapy-Induced Nausea and Vomiting**  
134                                    **— Single-Day High-Dose and Low-Dose Cisplatin Therapy<sup>1</sup>**

	KYTRIL Injection (mcg/kg)				P-Value (vs. 5 mcg/kg)		
	5	10	20	40	10	20	40
<b>High-Dose Cisplatin</b>							
Number of Patients	40	49	48	47			
Response Over 24 Hours							
Complete Response <sup>2</sup>	18%	41%	40%	47%	0.018	0.025	0.004
No Vomiting	28%	47%	44%	53%	NS	NS	0.016
No Nausea	15%	35%	38%	43%	0.036	0.019	0.005
<b>Low-Dose Cisplatin</b>							
Number of Patients	42	41	40	46			
Response Over 24 Hours							
Complete Response <sup>2</sup>	29%	56%	58%	41%	0.012	0.009	NS
No Vomiting	36%	63%	65%	43%	0.012	0.008	NS
No Nausea	29%	56%	38%	33%	0.012	NS	NS

135 <sup>1</sup> Cisplatin administration began within 10 minutes of KYTRIL Injection infusion and  
136 continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m<sup>2</sup> for low and  
137 high strata.

138 <sup>2</sup> No vomiting and no use of rescue antiemetic.

139 For both the low and high cisplatin strata, the 10, 20, and 40 mcg/kg doses were more  
140 effective than the 5 mcg/kg dose in preventing nausea and vomiting within 24 hours of  
141 chemotherapy administration. The 10 mcg/kg dose was at least as effective as the higher  
142 doses.

143 *Moderately Emetogenic Chemotherapy*

144 KYTRIL Injection, 40 mcg/kg, was compared with the combination of chlorpromazine  
145 (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately  
146 emetogenic chemotherapy, including primarily carboplatin >300 mg/m<sup>2</sup>, cisplatin 20 to  
147 50 mg/m<sup>2</sup> and cyclophosphamide >600 mg/m<sup>2</sup>. KYTRIL Injection was superior to the  
148 chlorpromazine regimen in preventing nausea and vomiting (see Table 6).

149 **Table 6**                    **Prevention of Chemotherapy-Induced Nausea and**  
150 **Vomiting—Single-Day Moderately Emetogenic**  
151 **Chemotherapy**

	<b>KYTRIL Injection</b>	<b>Chlorpromazine<sup>1</sup></b>	<b>P-Value</b>
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response <sup>2</sup>	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

152 <sup>1</sup> Patients also received dexamethasone, 12 mg.

153 <sup>2</sup> No vomiting and no moderate or severe nausea.

154 In other studies of moderately emetogenic chemotherapy, no significant difference in  
155 efficacy was found between KYTRIL doses of 40 mcg/kg and 160 mcg/kg.

156 **Repeat-Cycle Chemotherapy**

157 In an uncontrolled trial, 512 cancer patients received KYTRIL Injection, 40 mcg/kg,  
158 prophylactically, for two cycles of chemotherapy, 224 patients received it for at least four  
159 cycles, and 108 patients received it for at least six cycles. KYTRIL Injection efficacy  
160 remained relatively constant over the first six repeat cycles, with complete response rates  
161 (no vomiting and no moderate or severe nausea in 24 hours) of 60% to 69%. No patients  
162 were studied for more than 15 cycles.

163 **Pediatric Studies**

164 A randomized double-blind study evaluated the 24-hour response of 80 pediatric cancer  
165 patients (age 2 to 16 years) to KYTRIL Injection 10, 20 or 40 mcg/kg. Patients were  
166 treated with cisplatin ≥60 mg/m<sup>2</sup>, cytarabine ≥3 g/m<sup>2</sup>, cyclophosphamide ≥1 g/m<sup>2</sup> or  
167 nitrogen mustard ≥6 mg/m<sup>2</sup> (see Table 7).

168 **Table 7**            **Prevention of Chemotherapy-Induced Nausea and Vomiting**  
169 **in Pediatric Patients**

	<b>KYTRIL Injection Dose (mcg/kg)</b>		
	<b>10</b>	<b>20</b>	<b>40</b>
Number of Patients	29	26	25
Median Number of Vomiting Episodes	2	3	1
Complete Response Over 24 Hours <sup>1</sup>	21%	31%	32%

170 <sup>1</sup> No vomiting and no moderate or severe nausea.

171 A second pediatric study compared KYTRIL Injection 20 mcg/kg to chlorpromazine plus  
172 dexamethasone in 88 patients treated with ifosfamide  $\geq 3$  g/m<sup>2</sup>/day for two or three days.  
173 KYTRIL Injection was administered on each day of ifosfamide treatment. At 24 hours,  
174 22% of KYTRIL Injection patients achieved complete response (no vomiting and no  
175 moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine  
176 regimen. The median number of vomiting episodes with KYTRIL Injection was 1.5; with  
177 chlorpromazine it was 7.0.

## 178 **Postoperative Nausea and Vomiting**

### 179 **Prevention of Postoperative Nausea and Vomiting**

180 The efficacy of KYTRIL Injection for prevention of postoperative nausea and vomiting  
181 was evaluated in 868 patients, of which 833 were women, 35 men, 484 Caucasians, 348  
182 Asians, 18 Blacks, 18 Other, with 61 patients 65 years or older. KYTRIL was evaluated  
183 in two randomized, double-blind, placebo-controlled studies in patients who underwent  
184 elective gynecological surgery or cholecystectomy and received general anesthesia.  
185 Patients received a single intravenous dose of KYTRIL Injection (0.1 mg, 1 mg or 3 mg)  
186 or placebo either 5 minutes before induction of anesthesia or immediately before reversal  
187 of anesthesia. The primary endpoint was the proportion of patients with no vomiting for  
188 24 hours after surgery. Episodes of nausea and vomiting and use of rescue antiemetic  
189 therapy were recorded for 24 hours after surgery. In both studies, KYTRIL Injection (1  
190 mg) was more effective than placebo in preventing postoperative nausea and vomiting  
191 (see Table 8). No additional benefit was seen in patients who received the 3 mg dose.

192 **Table 8 Prevention of Postoperative Nausea and Vomiting in Adult**  
193 **Patients**

<b>Study and Efficacy Endpoint</b>	<b>Placebo</b>	<b>KYTRIL 0.1 mg</b>	<b>KYTRIL 1 mg</b>	<b>KYTRIL 3 mg</b>
<b>Study 1</b>				
<b>Number of Patients</b>	<b>133</b>	<b>132</b>	<b>134</b>	<b>128</b>
No Vomiting				
0 to 24 hours	34%	45%	63%**	62%**
No Nausea				
0 to 24 hours	22%	28%	50%**	42%**
No Nausea or Vomiting				
0 to 24 hours	18%	27%	49%**	42%**
No Use of Rescue Antiemetic Therapy				
0 to 24 hours	60%	67%	75%*	77%*
<b>Study 2</b>				
<b>Number of Patients</b>	<b>117</b>	–	<b>110</b>	<b>114</b>
No Vomiting				
0 to 24 hours	56%	–	77%**	75%*
No Nausea				
0 to 24 hours	37%	–	59%**	56%*

194 \*P<0.05

195 \*\*P<0.001 versus placebo

196 Note: No Vomiting = no vomiting and no use of rescue antiemetic therapy; No Nausea =  
197 no nausea and no use of rescue antiemetic therapy

198 **Gender/Race**

199 There were too few male and Black patients to adequately assess differences in effect in  
200 either population.

201 **Treatment of Postoperative Nausea and Vomiting**

202 The efficacy of KYTRIL Injection for treatment of postoperative nausea and vomiting  
203 was evaluated in 844 patients, of which 731 were women, 113 men, 777 Caucasians, 6  
204 Asians, 41 Blacks, 20 Other, with 107 patients 65 years or older. KYTRIL Injection was  
205 evaluated in two randomized, double-blind, placebo-controlled studies of adult surgical  
206 patients who received general anesthesia with no prophylactic antiemetic agent, and who  
207 experienced nausea or vomiting within 4 hours postoperatively. Patients received a single  
208 intravenous dose of KYTRIL Injection (0.1 mg, 1 mg or 3 mg) or placebo after  
209 experiencing postoperative nausea or vomiting. Episodes of nausea and vomiting and use  
210 of rescue antiemetic therapy were recorded for 24 hours after administration of study  
211 medication. KYTRIL Injection was more effective than placebo in treating postoperative  
212 nausea and vomiting (see Table 9). No additional benefit was seen in patients who  
213 received the 3 mg dose.

214  
215

**Table 9 Treatment of Postoperative Nausea and Vomiting in Adult Patients**

<b>Study and Efficacy Endpoint</b>	<b>Placebo</b>	<b>KYTRIL 0.1 mg</b>	<b>KYTRIL 1 mg</b>	<b>KYTRIL 3 mg</b>
<b>Study 3</b>				
<b>Number of Patients</b>	<b>133</b>	<b>128</b>	<b>133</b>	<b>125</b>
No Vomiting				
0 to 6 hours	26%	53%***	58%***	60%***
0 to 24 hours	20%	38%***	46%***	49%***
No Nausea				
0 to 6 hours	17%	40%***	41%***	42%***
0 to 24 hours	13%	27%**	30%**	37%***
No Use of Rescue Antiemetic Therapy				
0 to 6 hours	—	—	—	—
0 to 24 hours	33%	51%**	61%***	61%***
<b>Study 4</b>				
<b>Number of Patients (All Patients)</b>	<b>162</b>	<b>163</b>	—	—
No Vomiting				
0 to 6 hours	20%	32%*	—	—
0 to 24 hours	14%	23%*	—	—
No Nausea				
0 to 6 hours	13%	18%	—	—
0 to 24 hours	9%	14%	—	—
No Nausea or Vomiting				
0 to 6 hours	13%	18%	—	—
0 to 24 hours	9%	14%	—	—
No Use of Rescue Antiemetic Therapy				
0 to 6 hours	—	—	—	—
0 to 24 hours	24%	34%*	—	—
<b>Number of Patients (Treated for Vomiting)<sup>1</sup></b>	<b>86</b>	<b>103</b>	—	—
No Vomiting				
0 to 6 hours	21%	27%	—	—
0 to 24 hours	14%	20%	—	—

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\*P<0.05  
 \*\*P<0.01  
 \*\*\*P<0.001 versus placebo  
<sup>1</sup> Protocol Specified Analysis: Patients who had vomiting prior to treatment  
 Note: No vomiting = no vomiting and no use of rescue antiemetic therapy; No nausea = no nausea and no use of rescue antiemetic therapy

222 *Gender/Race*

223 There were too few male and Black patients to adequately assess differences in effect in  
224 either population.

225 **INDICATIONS AND USAGE**

226 KYTRIL Injection is indicated for:

- 227 • The prevention of nausea and/or vomiting associated with initial and repeat courses of  
228 emetogenic cancer therapy, including high-dose cisplatin.
- 229 • The prevention and treatment of postoperative nausea and vomiting. As with other  
230 antiemetics, routine prophylaxis is not recommended in patients in whom there is  
231 little expectation that nausea and/or vomiting will occur postoperatively. In patients  
232 where nausea and/or vomiting must be avoided during the postoperative period,  
233 KYTRIL Injection is recommended even where the incidence of postoperative nausea  
234 and/or vomiting is low.

235 **CONTRAINDICATIONS**

236 KYTRIL Injection is contraindicated in patients with known hypersensitivity to the drug  
237 or to any of its components.

238 **WARNINGS**

239 Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to  
240 other selective 5-HT<sub>3</sub> receptor antagonists.

241 **PRECAUTIONS**

242 KYTRIL is not a drug that stimulates gastric or intestinal peristalsis. It should not be used  
243 instead of nasogastric suction. The use of KYTRIL in patients following abdominal  
244 surgery or in patients with chemotherapy-induced nausea and vomiting may mask a  
245 progressive ileus and/or gastric distention.

246 **Drug Interactions**

247 Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme  
248 system in vitro. There have been no definitive drug-drug interaction studies to examine  
249 pharmacokinetic or pharmacodynamic interaction with other drugs; however, in humans,  
250 KYTRIL Injection has been safely administered with drugs representing  
251 benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with  
252 antiemetic treatments. KYTRIL Injection also does not appear to interact with  
253 emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic  
254 cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes  
255 may change the clearance and, hence, the half-life of granisetron. No specific interaction  
256 studies have been conducted in anesthetized patients. In addition, the activity of the  
257 cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main  
258 narcotic analgesic agents) is not modified by KYTRIL in vitro.

259 In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL.  
260 However, the clinical significance of in vivo pharmacokinetic interactions with  
261 ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction  
262 with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous  
263 KYTRIL. The clinical significance of this change is not known.

#### 264 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

265 In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or  
266 50 mg/kg/day (6, 30 or 300 mg/m<sup>2</sup>/day). The 50 mg/kg/day dose was reduced to  
267 25 mg/kg/day (150 mg/m<sup>2</sup>/day) during week 59 due to toxicity. For a 50 kg person of  
268 average height (1.46 m<sup>2</sup> body surface area), these doses represent 16, 81 and 405 times  
269 the recommended clinical dose (0.37 mg/m<sup>2</sup>, iv) on a body surface area basis. There was  
270 a statistically significant increase in the incidence of hepatocellular carcinomas and  
271 adenomas in males treated with 5 mg/kg/day (30 mg/m<sup>2</sup>/day, 81 times the recommended  
272 human dose based on body surface area) and above, and in females treated with  
273 25 mg/kg/day (150 mg/m<sup>2</sup>/day, 405 times the recommended human dose based on body  
274 surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day  
275 (6 mg/m<sup>2</sup>/day, 16 times the recommended human dose based on body surface area) in  
276 males and 5 mg/kg/day (30 mg/m<sup>2</sup>/day, 81 times the recommended human dose based on  
277 body surface area) in females. In a 12-month oral toxicity study, treatment with  
278 granisetron 100 mg/kg/day (600 mg/m<sup>2</sup>/day, 1622 times the recommended human dose  
279 based on body surface area) produced hepatocellular adenomas in male and female rats  
280 while no such tumors were found in the control rats. A 24-month mouse carcinogenicity  
281 study of granisetron did not show a statistically significant increase in tumor incidence,  
282 but the study was not conclusive.

283 Because of the tumor findings in rat studies, KYTRIL Injection should be prescribed only  
284 at the dose and for the indication recommended (see **INDICATIONS AND USAGE** and  
285 **DOSAGE AND ADMINISTRATION**).

286 Granisetron was not mutagenic in an in vitro Ames test and mouse lymphoma cell  
287 forward mutation assay, and in vivo mouse micronucleus test and in vitro and ex vivo rat  
288 hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa  
289 cells in vitro and a significant increased incidence of cells with polyploidy in an in vitro  
290 human lymphocyte chromosomal aberration test.

291 Granisetron at subcutaneous doses up to 6 mg/kg/day (36 mg/m<sup>2</sup>/day, 97 times the  
292 recommended human dose based on body surface area) was found to have no effect on  
293 fertility and reproductive performance of male and female rats.

#### 294 **Pregnancy**

##### 295 **Teratogenic Effects**

##### 296 *Pregnancy Category B.*

297 Reproduction studies have been performed in pregnant rats at intravenous doses up to  
298 9 mg/kg/day (54 mg/m<sup>2</sup>/day, 146 times the recommended human dose based on body  
299 surface area) and pregnant rabbits at intravenous doses up to 3 mg/kg/day

300 (35.4 mg/m<sup>2</sup>/day, 96 times the recommended human dose based on body surface area)  
301 and have revealed no evidence of impaired fertility or harm to the fetus due to  
302 granisetron. There are, however, no adequate and well-controlled studies in pregnant  
303 women. Because animal reproduction studies are not always predictive of human  
304 response, this drug should be used during pregnancy only if clearly needed.

305 Benzyl alcohol may cross the placenta. KYTRIL Injection 1 mg/1 mL is preserved with  
306 benzyl alcohol and should be used in pregnancy only if the benefit outweighs the  
307 potential risk.

### 308 **Nursing Mothers**

309 It is not known whether granisetron is excreted in human milk. Because many drugs are  
310 excreted in human milk, caution should be exercised when KYTRIL Injection is  
311 administered to a nursing woman.

### 312 **Pediatric Use**

313 See **DOSAGE AND ADMINISTRATION** for use in chemotherapy-induced nausea and  
314 vomiting in pediatric patients 2 to 16 years of age. Safety and effectiveness in pediatric  
315 patients under 2 years of age have not been established. Safety and effectiveness of  
316 KYTRIL Injection have not been established in pediatric patients for the prevention or  
317 treatment of postoperative nausea or vomiting.

318 Benzyl alcohol, a component of KYTRIL 1 mg/1 mL, has been associated with serious  
319 adverse events and death, particularly in neonates. The “gaspings syndrome,”  
320 characterized by central nervous system depression, metabolic acidosis, gasping  
321 respirations, and high levels of benzyl alcohol and metabolites in blood and urine, has  
322 been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low birth-  
323 weight neonates. Additional symptoms may include gradual neurological deterioration,  
324 seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic  
325 and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although  
326 normal therapeutic doses of this product deliver amounts of benzyl alcohol that are  
327 substantially lower than those reported in association with the “gaspings syndrome,” the  
328 minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature  
329 and low birth-weight infants, as well as patients receiving high dosages, may be more  
330 likely to develop toxicity. Practitioners administering this and other medications  
331 containing benzyl alcohol should consider the combined daily metabolic load of benzyl  
332 alcohol from all sources.

### 333 **Geriatric Use**

334 During chemotherapy clinical trials, 713 patients 65 years of age or older received  
335 KYTRIL Injection. Effectiveness and safety were similar in patients of various ages.

336 During postoperative nausea and vomiting clinical trials, 168 patients 65 years of age or  
337 older, of which 47 were 75 years of age or older, received KYTRIL Injection. Clinical  
338 studies of KYTRIL Injection did not include sufficient numbers of subjects aged 65 years  
339 and over to determine whether they respond differently from younger subjects. Other

340 reported clinical experience has not identified differences in responses between the  
341 elderly and younger patients.

342 **ADVERSE REACTIONS**

343 **Chemotherapy-Induced Nausea and Vomiting**

344 The following have been reported during controlled clinical trials or in the routine  
345 management of patients. The percentage figures are based on clinical trial experience  
346 only. **Table 10** gives the comparative frequencies of the five most commonly reported  
347 adverse events ( $\geq 3\%$ ) in patients receiving KYTRIL Injection, in single-day  
348 chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and  
349 intravenous fluids during the 24-hour period following KYTRIL Injection administration.  
350 Events were generally recorded over seven days post-KYTRIL Injection administration.  
351 In the absence of a placebo group, there is uncertainty as to how many of these events  
352 should be attributed to KYTRIL, except for headache, which was clearly more frequent  
353 than in comparison groups.

354 **Table 10**                    **Principal Adverse Events in Clinical Trials — Single-Day**  
355 **Chemotherapy**

	Percent of Patients With Event	
	KYTRIL Injection 40 mcg/kg (n=1268)	Comparator <sup>1</sup> (n=422)
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

356 <sup>1</sup> Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

357 In over 3,000 patients receiving KYTRIL Injection (2 to 160 mcg/kg) in single-day and  
358 multiple-day clinical trials with emetogenic cancer therapies, adverse events, other than  
359 those in **Table 10**, were observed; attribution of many of these events to KYTRIL is  
360 uncertain.

361 *Hepatic:* In comparative trials, mainly with cisplatin regimens, elevations of AST and  
362 ALT (>2 times the upper limit of normal) following administration of KYTRIL Injection  
363 occurred in 2.8% and 3.3% of patients, respectively. These frequencies were not  
364 significantly different from those seen with comparators (AST: 2.1%; ALT: 2.4%).

365 *Cardiovascular:* Hypertension (2%); hypotension, arrhythmias such as sinus bradycardia,  
366 atrial fibrillation, varying degrees of A-V block, ventricular ectopy including non-  
367 sustained tachycardia, and ECG abnormalities have been observed rarely.

368 *Central Nervous System:* Agitation, anxiety, CNS stimulation and insomnia were seen in  
369 less than 2% of patients. Extrapyrimal syndrome occurred rarely and only in the  
370 presence of other drugs associated with this syndrome.

371 *Hypersensitivity:* Rare cases of hypersensitivity reactions, sometimes severe (eg,  
372 anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

373 *Other:* Fever (3%), taste disorder (2%), skin rashes (1%). In multiple-day comparative  
374 studies, fever occurred more frequently with KYTRIL Injection (8.6%) than with  
375 comparative drugs (3.4%, P<0.014), which usually included dexamethasone.

376 **Postoperative Nausea and Vomiting**

377 The adverse events listed in **Table 11** were reported in  $\geq 2\%$  of adults receiving KYTRIL  
378 Injection 1 mg during controlled clinical trials.

379 **Table 11 Adverse Events  $\geq 2\%$**

	Percent of Patients With Event	
	KYTRIL Injection 1 mg (n=267)	Placebo (n=266)
Pain	10.1	8.3
Constipation	9.4	12.0
Anemia	9.4	10.2
Headache	8.6	7.1
Fever	7.9	4.5
Abdominal Pain	6.0	6.0
Hepatic Enzymes Increased	5.6	4.1
Insomnia	4.9	6.0
Bradycardia	4.5	5.3
Dizziness	4.1	3.4
Leukocytosis	3.7	4.1
Anxiety	3.4	3.8
Hypotension	3.4	3.8
Diarrhea	3.4	1.1
Flatulence	3.0	3.0
Infection	3.0	2.3
Dyspepsia	3.0	1.9
Hypertension	2.6	4.1
Urinary Tract Infection	2.6	3.4
Oliguria	2.2	1.5
Coughing	2.2	1.1

380 In a clinical study conducted in Japan, the types of adverse events differed notably from  
381 those reported above in **Table 11**. The adverse events in the Japanese study that occurred  
382 in  $\geq 2\%$  of patients and were more frequent with KYTRIL 1 mg than with placebo were:  
383 fever (56% to 50%), sputum increased (2.7% to 1.7%), and dermatitis (2.7% to 0%).

384 **OVERDOSAGE**

385 There is no specific antidote for KYTRIL Injection overdose. In case of overdose,  
386 symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron

387 hydrochloride injection has been reported without symptoms or only the occurrence of a  
388 slight headache.

### 389 **DOSAGE AND ADMINISTRATION**

390 NOTE: KYTRIL 1 MG/1 ML CONTAINS BENZYL ALCOHOL (see  
391 **PRECAUTIONS**).

#### 392 **Prevention of Chemotherapy-Induced Nausea and Vomiting**

393 The recommended dosage for KYTRIL Injection is 10 mcg/kg administered  
394 intravenously within 30 minutes before initiation of chemotherapy, and only on the  
395 day(s) chemotherapy is given.

#### 396 **Infusion Preparation**

397 KYTRIL Injection may be administered intravenously either undiluted over 30 seconds,  
398 or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes.

#### 399 *Stability*

400 Intravenous infusion of KYTRIL Injection should be prepared at the time of  
401 administration. However, KYTRIL Injection has been shown to be stable for at least 24  
402 hours when diluted in 0.9% Sodium Chloride or 5% Dextrose and stored at room  
403 temperature under normal lighting conditions.

404 As a general precaution, KYTRIL Injection should not be mixed in solution with other  
405 drugs. Parenteral drug products should be inspected visually for particulate matter and  
406 discoloration before administration whenever solution and container permit.

#### 407 **Pediatric Patients**

408 The recommended dose in pediatric patients 2 to 16 years of age is 10 mcg/kg (see  
409 **CLINICAL TRIALS**). Pediatric patients under 2 years of age have not been studied.

#### 410 **Geriatric Patients, Renal Failure Patients or Hepatically Impaired Patients**

411 No dosage adjustment is recommended (see **CLINICAL PHARMACOLOGY:**  
412 **Pharmacokinetics**).

#### 413 **Prevention and Treatment of Postoperative Nausea and Vomiting**

414 The recommended dosage for prevention of postoperative nausea and vomiting is 1 mg of  
415 KYTRIL, undiluted, administered intravenously over 30 seconds, before induction of  
416 anesthesia or immediately before reversal of anesthesia.

417 The recommended dosage for the treatment of nausea and/or vomiting after surgery is 1  
418 mg of KYTRIL, undiluted, administered intravenously over 30 seconds.

#### 419 **Pediatric Patients**

420 Safety and effectiveness of KYTRIL Injection have not been established in pediatric  
421 patients for the prevention or treatment of postoperative nausea or vomiting.

422 Geriatric Patients, Renal Failure Patients or Hepatically Impaired Patients  
423 No dosage adjustment is recommended (see **CLINICAL PHARMACOLOGY:**  
424 **Pharmacokinetics**).

425 **HOW SUPPLIED**

426 KYTRIL Injection, 1 mg/1 mL (free base), is supplied in 1 mL Single-Use Vials and 4  
427 mL Multi-Use Vials. CONTAINS BENZYL ALCOHOL.

428 NDC 0004-0239-09 (package of 1 Single-Use Vial)

429 NDC 0004-0240-09 (package of 1 Multi-Use Vial)

430 KYTRIL Injection, 0.1 mg/1 mL (free base), is supplied in 1 mL Single-Use Vials.  
431 CONTAINS NO PRESERVATIVE.

432 NDC 0004-0242-08 (package of 5 Single-Use Vials)

433 **Storage**

434 Store single-use vials and multi-use vials at 25°C (77°F); excursions permitted to 15° to  
435 30°C (59° to 86°F). [See USP Controlled Room Temperature]

436 Once the multi-use vial is penetrated, its contents should be used within 30 days.

437 Do not freeze. Protect from light.

438

439 Distributed by:



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