CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-239 /S007

Trade Name: Kytril Injection

Generic Name: granisetron HCl

Sponsor: Smithkline Beecham Pharmaceuticals

Approval Date: March 20, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239 /S007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 20-239/S-007

SmithKline Beecham Pharmaceuticals
Attention: Olivia Pinkett, Ph.D.
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

MAR 20 1997

Dear Dr. Pinkett:

We acknowledge your supplemental new drug application dated February 3, 1997, received February 4, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron HCl) Injection.

The User Fee goal date for this application is August 4, 1997.

The supplemental application provides for a revision to the DOSAGE AND ADMINISTRATION section of the package insert to include a word omitted from the final printed labeling approved with Supplements -002 and -004 on January 21, 1997. The last sentence in this section now reads (the added word has been underlined), "Kytril Injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% sodium Chloride or 5% Dextrose and infused over 5 minutes."

We have completed the review of this supplemental application and it is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Kati Johnson, Supervisory Consumer Safety Officer, at (301) 443-0487.

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-239
HFD-180/Div. files
HFD-180/CSO/K.Johnson

kj 3/19/97

DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)

Drafted by: kj/March 17, 1997/c:\wpfiles\cso\n\20239s07.0kj

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239 /S007

LABELING

RY.LO

MAR 20 1997

040 6

Labeling: _____

NDA No: _____ Rc'd. _____

Reviewed by: _____

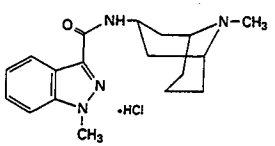
PRESCRIBING INFORMATION

KYTRIL®
granisetron hydrochloride Injection

040 6

DESCRIPTION

Kytril (granisetron hydrochloride) Injection is an antinauseant and antiemetic 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.

Each 1 mL of preservative-free aqueous solution contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1.0 mg and sodium chloride, 9.0 mg. The solution's pH ranges from 4.7 to 7.3.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B/C}$; 5-HT$_2$; for alpha$_1$-, alpha$_2$- or beta-adrenoreceptors; for dopamine-D$_2$; or for histamine-H$_1$; benzodiazepine; picrotoxin, or opioid receptors.

Serotonin receptors of the 5-HT$_3$ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT$_3$ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT$_3$ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

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

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

Pharmacokinetics

In adult cancer patients undergoing chemotherapy and in volunteers, infusion of a single 40 mcg/kg dose of *Kytril* Injection produced the following mean pharmacokinetic data:

Table 1. Pharmacokinetic Parameters in Adult Cancer Patients Undergoing Chemotherapy and in Volunteers, Following a Single Intravenous 40 mcg/kg Dose of Kytril (granisetron hydrochloride) Injection

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	Total Clearance (L/h/kg)	Volume of Distribution (L/kg)
Cancer Patients				
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
Volunteers				
21 to 42 years				
Mean	64.3†	4.91†	0.79†	3.04†
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†	7.69†	0.44†	3.97†
Range	14.6 to 153	2.65 to 17.7	0.17 to 1.06	1.75 to 7.01

*5-minute infusion.
†3-minute infusion.

There was high inter and intrasubject variability noted in these studies. No difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Animal studies suggest that some of the metabolites may also have 5-HT$_3$ receptor antagonist activity.

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

In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily.

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

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

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

Renal Failure Patients: Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 mcg/kg intravenous dose of *Kytril* Injection.

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

CLINICAL TRIALS

Kytril Injection has been shown to prevent nausea and vomiting associated with single-day and repeat cycle cancer chemotherapy.

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy: In a double-blind, placebo-controlled study in 28 cancer patients, *Kytril* Injection, administered as a single intravenous infusion of 40 mcg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy. See Table 2.

Table 2. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day Cisplatin Therapy[1]

	Kytril Injection	Placebo	*P*-Value
Number of Patients	14	14	
Response Over 24 Hours			
Complete Response[2]	93%	7%	<0.001
No Vomiting	93%	14%	<0.001
No More Than Mild Nausea	93%	7%	<0.001

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m^2 in the *Kytril* Injection group and 80 mg/m^2 in the placebo group.
2. No vomiting and no moderate or severe nausea.

Kytril Injection was also evaluated in a randomized dose response study of cancer patients receiving cisplatin ≥75 mg/m^2. Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydrazine, nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs and vinca alkaloids. *Kytril* Injection doses of 10 and 40 mcg/kg were superior to 2 mcg/kg in preventing cisplatin-induced nausea and vomiting, but 40 mcg/kg was not significantly superior to 10 mcg/kg. See Table 3.

Table 3. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day High-Dose Cisplatin Therapy[1]

	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[2]	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

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m^2.
2. No vomiting and no moderate or severe nausea.

Kytril (granisetron hydrochloride) Injection was also evaluated in a double-blind, randomized dose response study of 353 patients stratified for high (≥ 80 to 120 mg/m^2) or low (50 to 79 mg/m^2) cisplatin dose. Response rates of patients for both cisplatin strata are given in Table 4.

Table 4. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day High-Dose and Low-Dose Cisplatin Therapy[1]

	Kytril Injection (mcg/kg)				*P*-Value (vs. 5 mcg/kg)		
	5	10	20	40	10	20	40
High-Dose Cisplatin							
Number of Patients	40	49	48	47			
Response Over 24 Hours							
Complete Response[2]	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
Low-Dose Cisplatin							
Number of Patients	42	41	40	46			
Response Over 24 Hours							
Complete Response[2]	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

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m^2 for low and high strata.
2. No vomiting and no use of rescue antiemetic.

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

Moderately Emetogenic Chemotherapy: *Kytril* Injection, 40 mcg/kg, was compared with the combination of chlorpromazine (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately emetogenic chemotherapy, including primarily carboplatin >300 mg/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. *Kytril* Injection was superior to the chlorpromazine regimen in preventing nausea and vomiting. See Table 5.

Table 5. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day Moderately Emetogenic Chemotherapy

	Kytril Injection	Chlorpromazine[1]	*P*-Value
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response[2]	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

1. Patients also received dexamethasone, 12 mg.
2. No vomiting and no moderate or severe nausea.

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

Repeat-Cycle Chemotherapy

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

Pediatric Studies

A randomized double-blind study evaluated the 24-hour response of 80 pediatric cancer patients (age 2 to 16 years) to *Kytril* Injection 10, 20 or 40 mcg/kg. Patients were treated with cisplatin ≥60 mg/m^2, cytarabine ≥3 g/m^2, cyclophosphamide ≥1 g/m^2 or nitrogen mustard ≥6 mg/m^2. See Table 6.

Table 6. Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

	Kytril Injection Dose (mcg/kg)		
	10	20	40
Number of Patients	29	26	25
Median Number of Vomiting Episodes	2	3	1
Complete Response Over 24 Hours[1]	21%	31%	32%

1. No vomiting and no moderate or severe nausea.

A second pediatric study compared *Kytril* Injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide ≥3 g/m^2/day for two or three days. *Kytril* Injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of *Kytril* Injection patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine regimen. The median number of vomiting episodes with *Kytril* Injection was 1.5; with chlorpromazine it was 7.0.

INDICATIONS AND USAGE

Kytril (granisetron hydrochloride) Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

CONTRAINDICATIONS

Kytril Injection is contraindicated in patients with known hypersensitivity to the drug.

PRECAUTIONS

Drug Interactions

Granisetron does not induce d
drug-metabolizing enzyme s
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tility and reproductive perform

Pregnancy

Teratogenic Effects. Pregna
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based on body surface area) an
of impaired fertility or harm to
There are, however, no adequ
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ies are not always predictive o
should be used during pregnan

Nursing Mothers

It is not known whether grani
milk. Because many drugs are
tion should be exercised whe
tered to a nursing woman.

Pediatric Use

See DOSAGE AND ADMINISTI
to 16 years of age. Safety ar
under 2 years of age have not

Geriatric Use

During clinical trials, 713 patier
received Kytril (granisetron HCl)
safety were similar in patients

BING INFORMATION

'TRIL®
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ride) Injection is an antinauseant
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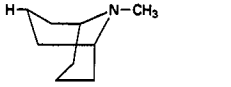
is:



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a white to off-white solid that
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sterile, nonpyrogenic, aqueous
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free aqueous solution contains
chloride equivalent to granise-
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5-hydroxytryptamine$_3$ (5-HT$_3$)
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HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B/C}$; 5-HT$_2$; for
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Volunteers				
21 to 42 years				
Mean	64.3†	4.91†	0.79†	3.04†
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†	7.69†	0.44†	3.97†
Range	14.6 to 153	2.65 to 17.7	0.17 to 1.06	1.75 to 7.01

*5-minute infusion.
†3-minute infusion.

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

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CLINICAL TRIALS

Kytril Injection has been shown to prevent nausea and vomiting associated with single-day and repeat cycle cancer chemotherapy.

Single-Day Chemotherapy

Cisplatin-Based Chemotherapy: In a double-blind, placebo-controlled study in 28 cancer patients, *Kytril* Injection, administered as a single intravenous infusion of 40 mcg/kg, was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin chemotherapy. See Table 2.

Table 2. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day Cisplatin Therapy[1]

	Kytril Injection	Placebo	*P*-Value
Number of Patients	14	14	
Response Over 24 Hours			
Complete Response[2]	93%	7%	<0.001
No Vomiting	93%	14%	<0.001
No More Than Mild Nausea	93%	7%	<0.001

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 1.5 to 3.0 hours. Mean cisplatin dose was 86 mg/m^2 in the *Kytril* Injection group and 80 mg/m^2 in the placebo group.
2. No vomiting and no moderate or severe nausea.

Kytril Injection was also evaluated in a randomized dose response study of cancer patients receiving cisplatin ≥75 mg/m^2. Additional chemotherapeutic agents included: anthracyclines, carboplatin, cytostatic antibiotics, folic acid derivatives, methylhydrazine, nitrogen mustard analogs, podophyllotoxin derivatives, pyrimidine analogs and vinca alkaloids. *Kytril* Injection doses of 10 and 40 mcg/kg were superior to 2 mcg/kg in preventing cisplatin-induced nausea and vomiting, but 40 mcg/kg was not significantly superior to 10 mcg/kg. See Table 3.

Table 3. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day High-Dose Cisplatin Therapy[1]

	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[2]	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

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 2.6 hours (mean). Mean cisplatin doses were 96 to 99 mg/m^2.
2. No vomiting and no moderate or severe nausea.

Kytril (granisetron hydrochloride) Injection was also evaluated in a double-blind, randomized dose response study of 353 patients stratified for high (≥ 80 to 120 mg/m^2) or low (50 to 79 mg/m^2) cisplatin dose. Response rates of patients for both cisplatin strata are given in Table 4.

Table 4. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day High-Dose and Low-Dose Cisplatin Therapy[1]

	Kytril Injection (mcg/kg)				*P*-Value (vs. 5 mcg/kg)		
	5	10	20	40	10	20	40
High-Dose Cisplatin							
Number of Patients	40	49	48	47			
Response Over 24 Hours							
Complete Response[2]	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
Low-Dose Cisplatin							
Number of Patients	42	41	40	46			
Response Over 24 Hours							
Complete Response[2]	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

1. Cisplatin administration began within 10 minutes of *Kytril* Injection infusion and continued for 2 hours (mean). Mean cisplatin doses were 64 and 98 mg/m^2 for low and high strata.
2. No vomiting and no use of rescue antiemetic.

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

Moderately Emetogenic Chemotherapy: *Kytril* Injection, 40 mcg/kg, was compared with the combination of chlorpromazine (50 to 200 mg/24 hours) and dexamethasone (12 mg) in patients treated with moderately emetogenic chemotherapy, including primarily carboplatin >300 mg/m^2, cisplatin 20 to 50 mg/m^2 and cyclophosphamide >600 mg/m^2. *Kytril* Injection was superior to the chlorpromazine regimen in preventing nausea and vomiting. See Table 5.

Table 5. Prevention of Chemotherapy-Induced Nausea and Vomiting—Single-Day Moderately Emetogenic Chemotherapy

	Kytril Injection	Chlorpromazine[1]	*P*-Value
Number of Patients	133	133	
Response Over 24 Hours			
Complete Response[2]	68%	47%	<0.001
No Vomiting	73%	53%	<0.001
No More Than Mild Nausea	77%	59%	<0.001

1. Patients also received dexamethasone, 12 mg.
2. No vomiting and no moderate or severe nausea.

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

Repeat-Cycle Chemotherapy

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

Pediatric Studies

A randomized double-blind study evaluated the 24-hour response of 80 pediatric cancer patients (age 2 to 16 years) to *Kytril* Injection 10, 20 or 40 mcg/kg. Patients were treated with cisplatin ≥60 mg/m^2, cytarabine ≥3 g/m^2, cyclophosphamide ≥1 g/m^2 or nitrogen mustard ≥6 mg/m^2. See Table 6.

Table 6. Prevention of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients

	Kytril Injection Dose (mcg/kg)		
	10	20	40
Number of Patients	29	26	25
Median Number of Vomiting Episodes	2	3	1
Complete Response Over 24 Hours[1]	21%	31%	32%

1. No vomiting and no moderate or severe nausea.

A second pediatric study compared *Kytril* Injection 20 mcg/kg to chlorpromazine plus dexamethasone in 88 patients treated with ifosfamide ≥3 g/m^2/day for two or three days. *Kytril* Injection was administered on each day of ifosfamide treatment. At 24 hours, 22% of *Kytril* Injection patients achieved complete response (no vomiting and no moderate or severe nausea in 24 hours) compared with 10% on the chlorpromazine regimen. The median number of vomiting episodes with *Kytril* Injection was 1.5; with chlorpromazine it was 7.0.

INDICATIONS AND USAGE

Kytril (granisetron hydrochloride) Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

CONTRAINDICATIONS

Kytril Injection is contraindicated in patients with known hypersensitivity to the drug.

PRECAUTIONS

Drug Interactions

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs, but in humans, *Kytril* Injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. *Kytril* Injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Because of the tumor findings in rat studies, Kytril (granisetron hydrochloride) Injection should be prescribed only at the dose and for the indication recommended (see INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

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

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

Pregnancy

Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m^2/day, 146 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 3 mg/kg/day (35.4 mg/m^2/day, 96 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

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

Pediatric Use

See DOSAGE AND ADMINISTRATION for use in children 2 to 16 years of age. Safety and effectiveness in children under 2 years of age have not been established.

Geriatric Use

During clinical trials, 713 patients 65 years of age or older received Kytril (granisetron HCl) Injection. Effectiveness and safety were similar in patients of various ages.

ADVERSE REACTIONS

The following have been reported during controlled clinical trials or in the routine management of patients. The percentage figures are based on clinical trial experience only. Table 7 gives the comparative frequencies of the five most commonly reported adverse events (≥3%) in patients receiving *Kytril* Injection, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following *Kytril* Injection administration. Events were generally recorded over seven days post-*Kytril* Injection administration. In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to *Kytril*, except for headache, which was clearly more frequent than in comparison groups.

Table 7. Principal Adverse Events in Clinical Trials—Single-Day Chemotherapy

	Percent of Patients with Event	
	***Kytril* Injection 40 mcg/kg** (n=1,268)	**Comparator[1]** (n=422)
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

1. Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

In over 3,000 patients receiving *Kytril* Injection (2 to 160 mcg/kg) in single-day and multiple-day clinical trials with emetogenic cancer therapies, adverse events, other than those in Table 7, were observed; attribution of many of these events to *Kytril* is uncertain.

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

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

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

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

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

OVERDOSAGE

There is no specific antidote for Kytril (granisetron hydrochloride) Injection overdosage. In case of overdosage, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride injection has been reported without symptoms or only the occurrence of a slight headache.

DOSAGE AND ADMINISTRATION

The recommended dosage for *Kytril* Injection is 10 mcg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given. *Kytril* Injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes.

Pediatric Use: The recommended dose in children 2 to 16 years of age is 10 mcg/kg (see CLINICAL TRIALS). Children under 2 years of age have not been studied.

Use in the Elderly, Renal Failure Patients or Hepatically Impaired Patients: No dosage adjustment is recommended. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Infusion Preparation

Kytril Injection, administered as a 5-minute infusion, should be diluted in 0.9% Sodium Chloride or 5% Dextrose to a total volume of 20 to 50 mL.

Stability

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

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

HOW SUPPLIED

Kytril (granisetron hydrochloride) Injection, 1 mg/mL (free base), is supplied in 1 mL Single-Use Vials, in packages of 1.

NDC 0029-4149-01 (package of 1)

Store vials at 30°C (86°F) or below. Do not freeze. Protect from light.

DATE OF ISSUANCE JAN. 1997

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

KY:L8 Printed in U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239 /S007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-239/S-007

Name of Drug: Kytril (granisetron Hcl) Injection

Sponsor: SmithKline Beecham Pharmaceuticals

MAR 19 1997

Material Reviewed

Submission Date(s): February 3, 1997

Receipt Date(s): February 4, 1997

Background and Summary Description:

The final printed labeling submitted upon which Supplements -002 and -004 were approved did not contain the word "over" in the last sentence of the DOSAGE AND ADMINISTRATION section;"Kytril Injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes."

Supplement -007, submitted as a "Special Supplement-Changes Being Effected" under 21 CFR 314.70© provides for this revision.

Review

The submitted labeling (KY:L8, Date of Issuance Jan. 1997) was compared to that approved with Supplements -002 and -004 on January 21, 1997 (KY:L7, Date of Issuance Dec. 1996). The only change made was that specified above.

Conclusions

An ACKNOWLEDGEMENT AND APPROVAL letter should be drafted.

Kate Johnson 3/19/97
Consumer Safety Officer

cc:
Original
HFD-180/Div. Files
HFD-180/KJohnson
draft: kj/March 17, 1997/c:\wpfiles\cso\n\20239s07.rkj
CSO REVIEW

3/19/97

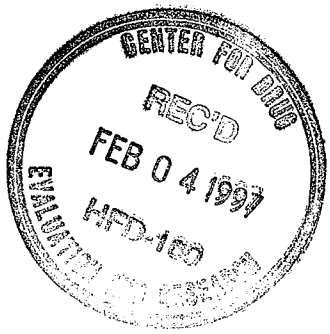
SmithKline Beecham
Pharmaceuticals

ORIGINAL

February 3, 1997

"Special Supplement - Changes Being Effected"

NDA 20-239
Kytril® (granisetron hydrochloride) Injection



Stephen B. Fredd, M.D., Director
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Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

NDA NO. 20239 REF. NO. 007
NDA SUPPL. NO. SLR

"Special Supplement - Changes Being Effected"

Dear Dr. Fredd:

Reference is made to our New Drug Application for Kytril (granisetron hydrochloride) Injection, which is approved for the prevention of nausea and vomiting associated with emetogenic cancer therapy.

This submission contains Final Printed Labeling, KY:L8. Specifically included are 16 copies of the prescribing information. Copies 1-8 are contained in the Archival copy; copies 9-16 are contained in the Review copy.

KY:L7 which was submitted on January 14, 1997, had the statement, **"...Kytril Injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused 5 minutes."** under the section DOSAGE AND

3/19/97

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

ADMINISTRATION. The statement has been revised to read **"...Kytril Injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% Sodium Chloride or 5% Dextrose and infused over 5 minutes."** The current PI in circulation is KY:L5 this submission and our submission dated January 14, 1997. We anticipate using KY:L8 beginning February 17, 1997.

Should you have any questions regarding the FPL, please do not hesitate to contact me at (610) 917-5840.

Sincerely,

Olivia Pinkett, Ph.D.
Director
U.S. Regulatory Affairs