CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-239/S018

Trade Name: Kytril Injection

Generic Name: (granisetron)

Sponsor: Hoffman-LaRoche Inc.

Approval Date: November 23, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S018

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S018

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-239/S-018

Hoffman-La Roche, Inc.
Attention: Anthony Corrado
Director of Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Mr. Corrado:

Please refer to your supplemental new drug application dated September 1, 2004, received September 8, 2004, submitted section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril® (granisetron) Injection.

We acknowledge receipt of your submissions dated March 2, 2005 and May 20, 2005.

Your submission of May 20, 2005 constituted a complete response to our March 8, 2005 action letter.

This supplemental new drug application provides for revisions to the Package Insert (PI), PRECAUTIONS section, Drug Interactions subsection.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

In the CLINICAL PHARMACOLOGY, Subpopulations, Geriatric subsection you revised the subsection heading from "Geriatric" to read "Elderly." However, the rest of the paragraph should be revised for consistent language as follows:

> ***"Elderly***
>
> *The ranges of the pharmacokinetic parameters in ~~geriatric~~ 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 ~~geriatric~~ elderly patients (see Table 1)."*

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling text for the Package Insert and submitted Package Insert (submitted May 20, 2005). These revisions are terms of the approval of this application.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved supplement NDA 20-239/S-018."** Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Betsy Scroggs, Regulatory Health Project Manager, at (301) 796-0991.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brian Harvey
11/23/2005 11:49:40 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S018

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-239/S-018

Hoffmann-LaRoche Inc.
Attention: Anthony Corrado
Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Corrado:

Please refer to your supplemental new drug application dated September 1, 2004, received September 8, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril® (granisetron) 1 mg/1 mL vial.

We acknowledge receipt of your submission dated March 2, 2005, received March 3, 2005.

This supplemental new drug application provides for changes to **Drug Interactions** sub-section of the **PRECAUTIONS** section of the package insert.

We completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, you must submit draft labeling revised as follows (as denoted by underlined and struck-through text):

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system *in vitro*. 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. No specific interaction studies have been conducted in anesthetized patients b(4) b(4) [1] In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL *in vitro*.*[2, 3, 4, 5]*

b(4) b(4) ~~In~~ in vitro human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL.[2] However, the clinical significance of *in vivo* pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous KYTRIL. The ~~clinical~~ significance of this changes is not known.[6] b(4)

In addition, all previous revisions as, reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

In addition, we request that you submit four copies of the introductory promotional materials you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application(s) under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call Melissa Hancock Furness, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Division Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick
3/8/05 12:23:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S018

LABELING

KYTRIL®

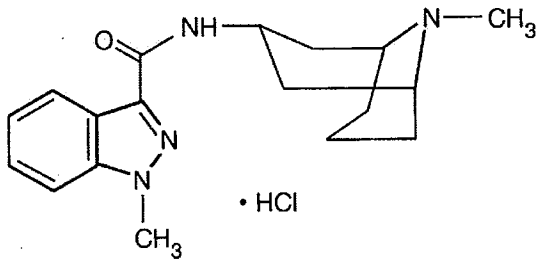
(granisetron hydrochloride)

INJECTION

Rx only

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 $C_{18}H_{24}N_4O$•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$_3$ (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 and may induce 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

Chemotherapy-Induced Nausea and Vomiting

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

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

Distribution

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

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. 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. Animal studies suggest that some of the metabolites may also have 5-HT_3 receptor antagonist activity.

Elimination

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.

Subpopulations

Gender

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

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 patients (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.

Postoperative Nausea and Vomiting

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

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

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

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

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting

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 3).

Table 3 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 4).

Table 4 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 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 5.

Table 5 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 6).

Table 6 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.

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 7).

Table 7 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.

Postoperative Nausea and Vomiting

Prevention of Postoperative Nausea and Vomiting

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

Table 8 Prevention of Postoperative Nausea and Vomiting in Adult Patients

Study and Efficacy Endpoint	Placebo	KYTRIL 0.1 mg	KYTRIL 1 mg	KYTRIL 3 mg
Study 1				
Number of Patients	**133**	**132**	**134**	**128**
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%*
Study 2				
Number of Patients	**117**	–	**110**	**114**
No Vomiting				
0 to 24 hours	56%	–	77%**	75%*
No Nausea				
0 to 24 hours	37%	–	59%**	56%*

*P<0.05

**P<0.001 versus placebo

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

Gender/Race

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

Treatment of Postoperative Nausea and Vomiting

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

Table 9 Treatment of Postoperative Nausea and Vomiting in Adult Patients

Study and Efficacy Endpoint	Placebo	KYTRIL 0.1 mg	KYTRIL 1 mg	KYTRIL 3 mg
Study 3				
Number of Patients	**133**	**128**	**133**	**125**
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%***
Study 4				
Number of Patients (All Patients)	**162**	**163**	**–**	**–**
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%*	–	–
Number of Patients (Treated for Vomiting)[1]	**86**	**103**	**–**	**–**
No Vomiting				
0 to 6 hours	21%	27%	–	–
0 to 24 hours	14%	20%	–	–

*P<0.05

**P<0.01

***P<0.001 versus placebo

[1] 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

Gender/Race

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

INDICATIONS AND USAGE

KYTRIL Injection is indicated for:

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

CONTRAINDICATIONS

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

WARNINGS

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

PRECAUTIONS

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

Drug Interactions

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system in vitro. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs; however, 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. No specific interaction studies have been conducted in anesthetized patients. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL in vitro.

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

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 (1.46 m^2 body surface area), these doses represent 16, 81 and 405 times the recommended clinical dose (0.37 mg/m^2, iv) 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 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 an 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.

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

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 chemotherapy-induced nausea and vomiting in pediatric patients 2 to 16 years of age. Safety and effectiveness in pediatric patients under 2 years of age have not been established. Safety and effectiveness of KYTRIL Injection have not been established in pediatric patients for the prevention or treatment of postoperative nausea or vomiting.

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

Geriatric Use

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

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

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

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting

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

	Percent of Patients With Event	
	KYTRIL Injection 40 mcg/kg (n=1268)	**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 10**, 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 non-sustained 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 (eg, 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.

Postoperative Nausea and Vomiting

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

Table 11 Adverse Events ≥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

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

OVERDOSAGE

There is no specific antidote for KYTRIL 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

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

Prevention of Chemotherapy-Induced Nausea and Vomiting

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.

Infusion Preparation

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.

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.

Pediatric Patients

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

Geriatric Patients, Renal Failure Patients or Hepatically Impaired Patients

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

Prevention and Treatment of Postoperative Nausea and Vomiting

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

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

Pediatric Patients

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

Geriatric Patients, Renal Failure Patients or Hepatically Impaired Patients

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

HOW SUPPLIED

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

NDC 0004-0239-09 (package of 1 Single-Use Vial)
NDC 0004-0240-09 (package of 1 Multi-Use Vial)

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

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

Storage

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

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

Do not freeze. Protect from light.

Distributed by:

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

xxxxxxxx

xxxxxxxxUSA

Revised: Month Year

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S018

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-239/SLR-018 SUBMISSION DATE: 09/01/04
Granisetron HCl Injection, 1 mg/mL

BRAND NAME: Kytril®

SPONSOR: Hoffman-La Roche, Inc. REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Labeling Supplement

BACKGROUND:

Kytril (granisetron HCl, 1 mg/mL) Injection was approved by the Agency on 05/11/94. It is indicated for **1)** the prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin and **2)** the prevention and treatment of postoperative nausea and vomiting.

On 09/01/04, Roche submitted labeling supplement SLR-018 to NDA 20-239 proposing changes to the Drug Interactions subsection of the Precautions section. Changes are not proposed to the Pharmacokinetics subsection under CLINICAL PHARMACOLOGY section. The proposed changes are shown below:

The second and third paragraphs under Drug Interaction subsection of PRECAUTIONS Section;

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. No specific interaction studies have been conducted in anesthetized patients [redacted] b(4) b(4) [1] In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified [redacted] b(4)

[redacted] b(4) b(4) b(4) The clinical significance of changes is not known.

Above changes were supported by the sponsor from information contained in four study reports (#1, 2, 3, and 6) and two published articles (# 4 and #5) as shown below;

1. Granisetron Hydrochloride (IV) Post-Operative Nausea and Vomiting, Part IC.3, Clinical Expert Report. March 1995.

2. Bloomer JC, et al. An *in vitro* investigation of the potential for drug interactions involving BRL 43694 and the human cytochrome P450 isoenzymes 1A2, 2A6, 2C8-9, 2C18, 2D6, 2E1 and 3A. Report No. BF-1011/BRL-043694/2. NDA 20-239. June 25, 1993. Vol. 67: 1-79.

3. Baldwin SJ, et al. An *in vitro* investigation into the inhibitory potential of BRL 43694, ondansetron, tropisetron, Y-25130 and BRL 46470 on the human cytochrome P450s 1A2, 2A6, 2B6, 2C8-9, 2C19, 2D6, 2E1, 3A and 4A. Report No. BF-1020/BRL-043694/1. NDA 20-239. April 19, 1994. Vol. 67: 80-130.

4. Bloomer JC, Baldwin SJ, Smith GJ, et al. Characterization of the cytochrome P450 enzymes involved in the *in vitro* metabolism of granisetron. Br. J. Clin. Pharmacol. 1994; 38: 557-566.

5. Gregory RE, Ettinger DS. 5-HT_3 Receptor Antagonists for the Prevention of Chemotherapy-Induced Nausea and Vomiting. A Comparison of Their Pharmacology and Clinical Efficacy. Drugs. February 1998; 55 (2): 173-189.

6. Lang U, et al. Single intravenous dose pharmacokinetics of BRL 43694A (granisetron) in healthy male volunteers before and after potential liver enzyme induction caused by repeated oral dosing of phenobarbital. Study reference 43694A/033/NE/001/Kurth. August 1991.

Study report # 1 is related to clinical safety update and article # 5 is a review article comparing the pharmacology and clinical efficacy of granisetron with other 5-HT_3 receptor antagonists (these will be deferred to the reviewing medical officer). Two study reports (#2 and #3), related to the identification of cytochrome P450 isoenzymes, were reviewed previously. Article # 4 is a publication based on the above two mentioned study reports (# 2 and 3). Study Report # 6 is to examine the effect of liver enzyme induction caused by repeated oral dosing of phenobarbital of a single IV dose of granisetron.

Therefore, article # 4 and study report # 6 will be reviewed.

DISCUSSION:

1. #4: ***Bloomer JC, Baldwin SJ, Smith GJ, et al. Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of granisetron. Br. J. Clin. Pharmacol. 1994; 38: 557-566.***

   In this study, *in vitro* metabolism of granisetron was investigated in human liver microsomes to identify the specific forms of cytochrome P450 responsible for the major metabolites, 7 –OH and 9'-desmethyl- granisetron.

   Specific P450 inhibitors such as, quinidine (CYP2D6), sulphaphenazine (CYP2C8-9), and furafylline (CYP1A2), ketoconazole (CYP3A4) and the substrate (testosterone) were further used to indicate the extent of involvement.

   The activities of CYP P450 isoenzymes, ethoxyresorufin O-deethylase (CYP1A2), coumarin 7-hydroxylase (2A6), 7-ethody-4-trifluoromethyl coumarin (2B6), tolbutamide

hydroxylase (2C8-9), S-mephenytoin 4-hydroxylase (2C19), bufuralol 1'-hydroxylase (2D6), chlorzoxazone 6-hydroxylase (2E1), and testosterone 6β-hydroxylase (3A), were determined in the presences of granisetron for its inhibitory potential.

The conclusion from this study was that CYP 3A was involved in the metabolism of granisetron and that granisetron caused no inhibition (IC_{50} > 250 μM) of the cytochrome P450 enzymes investigated (CYP1A2, 2A6, 2B6, 2C8-9, 2C19, 2D6, 2E1, and 3A).

2. #6: ***Lang U, et al. Single intravenous dose pharmacokinetics of BRL 43694A (granisetron) in healthy male volunteers before and after potential liver enzyme induction caused by repeated oral dosing of phenobarbital. Study reference 43694A/033/NE/001/Kurth. August 1991.***

In this study, pharmacokinetics (PK) of a single IV dose (a 5-min infusion; 4 μg/kg) of granisetron on Days 1 and 15 was studied in healthy male volunteers (n=16; 21-39 yrs old) before and after potential liver induction caused by repeated oral dosing of phenobarbital (100 mg tablet given QD for 14 days).

Plasma samples were obtained at predose, at the end of infusion, at 2, 5, 10, 15, 20, 30, 45, 60 min, and at 1.5, 2, 3, 4, 6, 8, 12, post infusion for granisetron assay and its subsequent PK analysis.

Granisetron had 25% higher clearance, slightly higher volume of distribution (13% ↑) and shorter half-life (10% ↓) on day 1 compared to those on Day 15. Co-administration of Phenobarbital with granisetron increased the CL of granisetron, however, these changes in PK may not have significant clinical consequences.

LABELING COMMENTS: (Need to be sent to the sponsor)

Under Drug Interaction subsection of PRECAUTIONS Section;

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system *in vitro*. 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. No specific interaction studies have been conducted in anesthetized patients [redacted] In b(4)

b(4)

addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL *in vitro*.[2, 3, 4, 5]

In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL.[2] However, the clinical significance of *in vivo* pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous KYTRIL. The clinical significance of this change is not known.[6]

RECOMMENDATION:

From the Office of Clinical Pharmacology and Biopharmaceutics perspective, supplement SLR-018 to NDA 20-239 is acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the Package Insert. The above labeling revision should be conveyed to the sponsor.

02/25/05
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

Team Leader
Suresh Doddapaneni, Ph.D. 03/02/05

NDA 20-239 (SLR-018) for Kytril (Granisetron HCl; 1 mg/mL) Injeciton

Appendix

Sponsor Proposed Annotated Labeling (09/01/04)

17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

___✓___ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*20-239
5018

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tien-Mien Chen
3/4/05 10:12:51 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/4/05 11:03:13 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY HEALTH PROJECT MANAGER REVIEW

Application Number: NDA 20-239/SLR-018

Name of Drug: Kytril® (granisetron) 1 mg/1 mL vial

Sponsor: Hoffman-LaRoche

Material Reviewed

Submission Date(s): September 1, 2004

Receipt Date(s): September 8, 2004

Background and Summary Description

NDA 20-239 for Kytril® Injection was approved December 29, 1993 for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy. Supplement SE1-008 was approved August 16, 2002 for the prevention and treatment of postoperative nausea and vomiting.

The last approved label, Supplement SCF-015, provided for: 1) a change in formulation to the 1 mg/1 mL injectable dosage form to include the addition of benzyl alcohol; 2) updating the label to strengthen standard language for drug products containing benzyl alcohol (per the Agency's March 29, 2004 supplement request letter).

The currently proposed label, NDA 20-239/SLR-018, proposes changes to **Drug Interactions** sub-section of the **PRECAUTIONS** section of the Package insert.

Review

1. The proposed labeling (XXXXXXXXX, S-018, dated: 09/01/04, received: 09/08/04) was compared electronically to the currently approved labeling (27898612, S-015, dated: 04/20/04, received: 04/22/04, approved: 08/20/04). All proposed changes were indicated in the sponsor's annotated proposed label. The *proposed changes* were as follows, and are noted by *underline*:

   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. No specific interaction studies have been conducted in anesthetized patients, b(4)

[1] In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by I b(4) b(4) b(4) b(4) *The clinical significance of changes is not known.* b(4)

2. The proposed label was reviewed by the Biopharmaceutics Reviewer, Dr. Tien Mien Chen. Dr. Chen recommended the following changes to firm's proposed label in his 03/03/05 review which are denoted by underlined and ~~struck-through~~ text:

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system in vitro. 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. No specific interaction studies have been conducted in anesthetized patients b(4) *[1] In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL in vitro.[2, 3, 4, 5]* b(4) b(4) In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL.[2] However, the clinical significance of in vivo pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous KYTRIL. The clinical significance of this changes is not known.[6] b(4)

3. In addition, the proposed label has been reviewed by the Clinical Reviewer, Dr. Gary Della'Zanna. Dr. Della'Zanna indicated verbally to me on 03/04/05 that he agreed with Dr. Chen's above recommendations and also recommended the following additional change which is noted by ~~struck-through~~ text below:

No specific interaction studies have been conducted in anesthetized patients b(4) b(4)

Conclusions

1. The revised draft package insert submitted on September 1, 2004 is not acceptable.

2. An approvable letter should be sent to the sponsor.

Melissa Hancock Furness, B.S.
Regulatory Project Manager

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

Gary Della'Zanna, D.O.
Medical Officer

Hugo Gallo-Torres, M.D., Ph.D.
Medical Team Leader

Drafted: MHF 03/02/05
Revised/Initialed: BS 03/04/05
Finalized:
Filename: Kytri_PM_LabelingReview_N20-239_S-018.doc

RPM LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melissa Furness
3/8/05 11:01:50 AM
CSO

Julieann DuBeau
3/8/05 11:04:50 AM
CSO
Signing for Brian Strongin, co-CPMS.

Gary DellaZanna
3/8/05 11:08:24 AM
MEDICAL OFFICER

Ruyi He
3/8/05 11:19:51 AM
MEDICAL OFFICER
Signing for Hugo Gallo-Torres

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY HEALTH PROJECT MANAGER REVIEW

Application Number: NDA 20-239/SLR-018/AL

Name of Drug: Kytril® (granisetron) Injection, 1 mg/ 1 mL and 0.1 mg/ 1 mL

Sponsor: Hoffman-LaRoche, Inc.

Material Reviewed

Submission Dates	Receipt Dates
September 1, 2004	September 8, 2004
March 2, 2005	March 3, 2005
May 20, 2005	May 23, 2005

Background and Summary Description

Kytril® (granisetron hydrochloride) Injection, NDA 20-239, approved December 29, 1993, provided for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy.

Supplement SE1-008 approved August 16, 2002, provided for the prevention and treatment of postoperative nausea and vomiting.

Supplement SCF-015, approved August 20, 2004, provided for: 1) a change in formulation to the 1 mg/1 mL injectable dosage form to include the addition of benzyl alcohol, and 2) an update to the label to strengthen standard language for drug products containing benzyl alcohol (per the Agency's March 29, 2004 supplement request letter).

Supplement SCF-016, approved September 17, 2004, provided for the addition of a 0.1 mg/1 mL single-use vial.

Supplement, SLR-018, submitted September 1, 2004, provided for changes to the Package Insert (PI), PRECAUTIONS, Drug Interactions subsection.

The March 3, 2005 Biopharmaceutics review recommended the following changes to the firm's proposed Injection label which are denoted by underlined and ~~struck-through~~ text:

> "Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system in vitro. 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. No specific interaction studies have been conducted in anesthetized patients, b(4)

b(4) In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL in vitro.[2, 3, 4, 5]

b(4) b(4) In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of KYTRIL.[2] However, the clinical significance of in vivo pharmacokinetic interactions with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of intravenous KYTRIL. The clinical significance of this changes is not known.[6]" b(4)

Additionally, the March 4, 2005 verbal Clinical communication to the Project Manager recommended the following revision:

"No specific interaction studies have been conducted in anesthetized patients b(4) b(4)

The March 8, 2005 RPM labeling review recommended the above and was co-signed by the disciplines noted above.

Our March 8, 2005 approvable letter (faxed and mailed) communicated our conclusion that the firm's revised draft package insert submitted September 1, 2004 was not acceptable and contained our revisions noted above.

The sponsor's Complete Response to our March 8, 2005 approvable letter, submitted May 20, 2005 (in the same cover letter as the Kytril® Injection) received May 23, 2005, states "the Sponsor accepts the revisions made by FDA within the fax and is herein submitting draft labeling which includes those changes."

The sponsor also notes that the amended version of the Kytril® USPI for the injection now reflects our September 17, 2004 approval of NDA 20-293/SCF-016 which provided fro the addition of a 0.1 mg/1 mL single-use vial.

Review

The proposed draft package insert (XXXXXXX, S-018/AL, dated: May 20, 2005, received May 24, 2005 was compared to the currently approved labeling (identified as 27898822, Revised: September 2004, SCF-016, approved September 17, 2004).

All requested changes were indicated in the Sponsor's annotated proposed PI including a few minor editorial revisions.

Package Insert

1. CLINICAL PHARMACOLOGY, Subpopulations, Geriatric subsection

   The subsection heading was revised from "Geriatric" to read "Elderly".

   Comment: This revision is consistent with the PI, CLINICAL PHARMACOLOGY, Subpopulations, Geriatric subsection for NDA 20-305/SLR-010, Kytril® (granisetron

hydrochloride) Tablets and NDA 21-238/SLR-005 Kytril® (granisetron hydrochloride) Oral Solution, also submitted September 1, 2004. However, the rest of the paragraph should be revised to harmonize with the Package Inserts noted above as follows:

Elderly

The ranges of the pharmacokinetic parameters in ~~geriatric~~ 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 ~~geriatric~~ elderly patients (see Error! Reference source not found.).

2. PRECAUTIONS, Drug Interactions sub-section

   The sponsor made all FDA advised revisions to the **PRECAUTIONS**, Drug Interactions sub-section as communicated in our March 8, 2005 approvable letter. In addition, the sponsor made minor editorial revisions that do not change the context of the label and are reportable in an annual report.

   Comment: The sponsor has done what we asked the sponsor to do and is acceptable.

Conclusions

1. The revised draft package insert submitted May 20, 2005 is acceptable.

2. An approval letter should be sent to the sponsor with the request for the minor editorial revisions as noted above in #1.

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: BHS 11-16-2005
Revised/Initialed: JD 11-18-2005
Finalized: BHS 11-21-2005
Filename: C:\CDERAPPS\Data\My Documents\Kytril SLRs\Injection\FINAL bhs Kytri_PM_Labeling Review_Inj N20-239_S-018AL.doc
RPM LABELING REVIEW

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/s/

Betsy Scroggs
11/21/2005 04:04:39 PM
CSO

Julieann DuBeau
11/21/2005 04:34:09 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-305/S-010
NDA 21-238/S-005
NDA 20-239/S-018

Hoffman-La Roche Inc.
Attention: Anthony J. Corrado
Director of Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Corrado

We acknowledge receipt on May 23, 2005 of your May 20, 2005 resubmission to your supplemental new drug applications for the following:

NDA 20-305/S-010 Kytril® (granisetron) Tablets
NDA 21-238/S-050 Kytril® (granisetron) Oral Solution
NDA 20-239/S-018 Kytril® (granisetron) Injection

These amended submissions constitute a complete response to our March 14, 2005 action letters and provide for changes to the PRECAUTIONS section and Drug Interactions sub-section of the respective package inserts. The user fee goal date is November 23, 2005 for each of these applications.

If you have any question, call me at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm. D.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Betsy Scroggs
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-238/S-005
NDA 20-239/S-018
NDA 20-305/S-010

PRIOR APPROVAL SUPPLEMENT

Hoffman-La Roche Inc.
Attention: Anthony J. Corrado
Director, DRA
340 Kingsland Street
Bldg 1, 2nd Floor
Nutley, NJ 07110-1100

Dear Mr. Corrado:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of drug product	NDA number	Supplement number
Kytril® (granisetron hydrochloride) Oral Solution, 2 mg/10 mL	21-238	005
Kytril® (granisetron hydrochloride) Injection, 0.1 mg/1 mL, 1 mg/1 mL, 4 mg/4 mL	20-239	018
Kytril® (granisetron hydrochloride) Tablets, 1 mg	20-305	010

Date of supplement: September 1, 2004

Date of receipt: September 8, 2004

These supplemental applications propose to update the PRECAUTIONS, Drug Interaction section of the label for each NDA respectively.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 7, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 8, 2005.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/US Overnight mail
Dr. Joyce Korvick, Acting Division Director
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products
Attention: Document Control Room 8th Floor
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Betsy Scroggs
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