CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-239/S015

Trade Name: Kytril Injection 1mg/mL

Generic Name: (granisetron)

Sponsor: Hoffman-LaRoche, Inc.

Approval Date: August 20, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-239/S-015

Hoffmann-LaRoche Inc.
Attention: Kathleen Schostack, Ph.D.
Group Director, Technical Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Schostack:

Please refer to your supplemental new drug application dated December 22, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril® (granisetron) Injection, 1 mg/1 mL.

We acknowledge receipt of your submission dated April 20, 2004 received April 22, 2004.

Your submission of April 20, 2004 constituted a complete response to our November 14, 2003 action letter.

This supplemental new drug application provides for addition of benzyl alcohol to the 1 mg/1 mL single-dose vial and revision of the labeling to add precautions concerning the benzyl alcohol.

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.

The final printed labeling (FPL) must be identical to the enclosed package insert (19apr2004) submitted electronically April 20, 2004.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

This submission should be designated "FPL for approved supplement NDA 20-239/S-015." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that 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

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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, Pharm. D., Consumer Safety Officer at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug 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/

Robert Justice
8/20/04 11:31:50 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S015

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-239/S-015

Hoffman-La Roche Inc.
Attention: Sarah Orris
Program Manager
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Ms. Orris:

Please refer to your supplemental new drug applications dated July 11, 2003 received July 14, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril® (granisetron) 1 mg/1 mL Injection.

We also refer to the telephone conversation this morning between Mr. Brian Strongin, Supervisory Regulatory Project Manager, Dr. Betsy Scroggs, Consumer Safety Officer, of this Division and yourself in which they acknowledged and described, the need to administratively split the 1 mg/1 mL Injection (now designated as Supplement-015) [redacted] since different actions would be taken in regard to the request for [redacted] vial size. The other supplements [redacted] are addressed under separate cover.

This supplemental new drug application provides for a change in the formulation for the 1 mg/1 mL Injection.

We completed our review of this supplemental application and it is approvable. Before this supplement may be approved, however, you must address the following deficiency:

> From a scientific and regulatory point of view, addition of benzyl alcohol to the single dose vial (1 mg/1 mL) is not justified. The original formulation should be retained.

Within 10 days after the date of this letter, you are required to amend this supplemental 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 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.

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

If you have any questions call, Dr. Betsy Scroggs, Consumer Safety Officer at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
11/14/03 05:28:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S015

LABELING

Roche

KYTRIL®

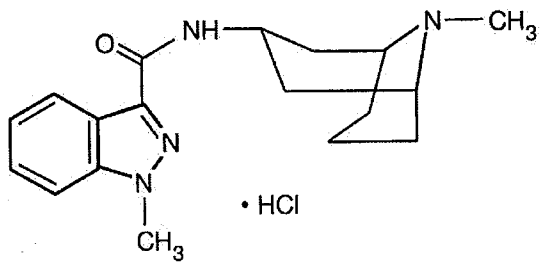
(granisetron hydrochloride)

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 is available in 1 mL single-dose and 4 mL multi-dose vials.

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.

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.

Geriatrics

The ranges of the pharmacokinetic parameters in geriatric 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 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

KYTRIL® (granisetron hydrochloride)

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.

KYTRIL® (granisetron hydrochloride)

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.

KYTRIL® (granisetron hydrochloride)

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. 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 (1.46 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. Granisetron injection preserved with benzyl alcohol 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 this drug product, 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.

KYTRIL® (granisetron hydrochloride)

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: CONTAINS BENZYL ALCOHOL (see **PRECAUTIONS**).

KYTRIL® (granisetron hydrochloride)

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**).

KYTRIL® (granisetron hydrochloride)

HOW SUPPLIED

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

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

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

Storage

Store single-dose vials and multi-dose 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-dose 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

Revised: Month Year

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239 /S015

CHEMISTRY REVIEW(S)

Memorandum:

From: Ramesh Raghavachari, Ph.D. - Review Chemist

Through: Liang Zhou - Chemistry Team Leader
Betsy Scroggs - Project Manager

To: NDA # 20-239 – S-015

Subject: Kytril (granisetron.HCl) injection- Addition of Benzyl alcohol to 1 mg/1mL single dose vial

Date: February 10, 2004

Background:

Kytril injection product has been recently transferred from GSK to Roche. This change has warranted the transfer of the manufacturing facilities to Roche. The EER for the new manufacturing site has been found to be acceptable by the Office of Compliance. The supplement (S-015) had also proposed a formulation change to include benzyl alcohol in 1mg/1mL injection vial. The manufacturer has 2 doses 1mg/1mL single dose vial and the 4mg/4mL multiple dose vials. The 4mg/4mL vial contains benzyl alcohol as a preservative as approved. The approved form of 1 mg/1mL single dose vial does not contain benzyl alcohol. The applicant requests to reformulate this 1mg/1mL vial product to contain benzyl alcohol. This request has been made to facilitate the transfer and maintain only one formulation. This supplement was recommended 'approvable' requesting the applicant to retain original formulation. The original formulation for 1mg/1mL vial should be retained due to the USP compendial recommendations, which does not require preservatives for single dose vials. Further, if benzyl alcohol is used in 1mg/1mL vials there is a possibility that the practitioners may use in neonatal and pediatric patients. The applicant did not provide scientific or regulatory justification for this formulation change, hence the supplement was 'approvable (AE). Justification for the change in formulation appears to be a and

In view of the AE letter, the applicant had requested a teleconference to discuss the issue.

Chemistry Comments:

The medical team was informally consulted via email through the project manager. The medical team after review of the file, has recommended allowing the addition of benzyl alcohol in the 1mg/1mL single dose vial with the revision of the label and the packaging insert. In addition, informal discussions with Dr. Peter Cooney from the Microbiology (through the ONDC management Dr. Eric Duffy) regarding this review policy matter suggested that, there was precedence in this case with respect to other drug products.

Conclusion:

The change in formulation for the addition of benzyl alcohol in the 1mg/1mL single dose vial may be approved, if the applicant submits a revision of the labeling for this product as recommended by the medical team.

The labeling changes suggested by the medical team should be conveyed to the applicant. Therefore, no teleconference would be needed at this time.

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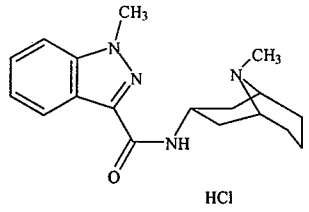
/s/

Ramesh Raghavachari
2/12/04 10:07:17 AM
CHEMIST
This is a Memo for the telecon request from the applicant for change in formulation to add Benzyl alcohol in the 1mg/1mL single dose vial.

Liang Zhou
2/12/04 10:20:53 AM
CHEMIST

CHEMIST'S REVIEW 3	1. Organization: HFD-180	2. NDA Number: 20-239
3. Name and Address of Applicant (City & State): Hoffmann-La Roche Inc. 340 Kingland Street Nutley, NJ 07110-1199		4. AF Number:
		Supplement(s)
6. Name of Drug: Kytril	7. Nonproprietary Name: Granisetron Hydrochloride	Number(s): [redacted] SCF-015 / Date(s): July 11, 2003
8. Supplement Provides for retaining the change in formulation with the addition of benzyl alcohol in the 1 mg/1 mL single dose vial Kytril injection and revise labeling.		9. Amendments and Other (Reports, etc.) Dates: SCF-015-AC April 20,2004
10. Pharmacological Category: Anti-emetic	11. How Dispensed: Rx	12. Related IND/NDA/DMF(s): None
13. Dosage Form: Injection-Intravenous	14. Potency: 1 mg/mL & 4mg/4mL	
15. Chemical Name and Structure:  *endo* -N-(9-methyl-9- azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride		16. Records and Reports: Current Yes No / Reviewed Yes x No

17. Comments: See Review Notes.

HFD-180/Div File
HFD-181/CSO/bstrongin
HFD-180/rjustice
HFD-180/rraghavachari
R/D init by:lzhou

18. Conclusions and Recommendations: *This supplement may be approved based on CMC point of view.*

19. Reviewer

Name:	Signature	Date Completed:
Ramesh Raghavachari		May 21, 2004

3 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-239
S015

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/s/

Ramesh Raghavachari
5/24/04 11:34:17 AM
CHEMIST

Liang Zhou
5/24/04 11:42:28 AM
CHEMIST
Betsy: This requires DD signature pending MO consult /labeling review.

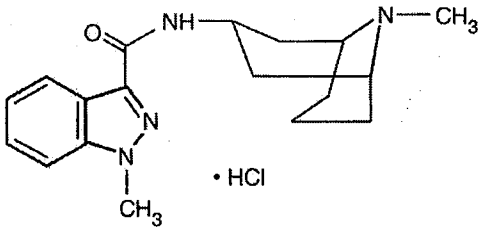
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S015

MEDICAL REVIEW(S)

Granisetron



NDA:	20-239 /S-015
Chemical Name:	Granisetron HCl
Class:	5-HT_3-receptor antagonist
Date:	July 28, 2004
Applicant:	Roche Inc.
Documents Reviewed:	Chemistry review Applicant Proposed Labeling Changes
Division Director:	Robert Justice M.D.
Acting Team Leader:	Ruyi He M.D.
Medical Officer:	Gary Della'Zanna D.O. M.Sc.
Project Manager:	Betsy Scroggs Ph.D

Benzyl Alcohol

Background:

Granisetron Injection was first approved in December 1993 for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric and adult patients. Granisetron Tablets were approved March 1995 to treat adult patients with CINV, and in July 1999 received approval for prevention of adult radiation-induced nausea and vomiting (RINV). In June 2001, Granisetron Oral Solution was approved for treatment of adult patients with CINV or RINV. In August 2002, granisetron injection was then approved for the prevention and treatment of postoperative nausea and vomiting (PONV).

Presently, intravenous granisetron is available in two formulations, a 1mg/1ml single dose vial, and a 4mg/4ml multi-dose vial. The *approved* 4mg/4ml multi-dose vial includes benzyl alcohol as a preservative. The Applicant proposed a formulation change to the 1mg/1ml single dose vial to be the same as the 4mg/4ml multi-dose vial.

Medical Officer Comment:
The proposed change in formulation should be approved. The Applicant has revised the label to include standard language for drug products containing benzyl alcohol.

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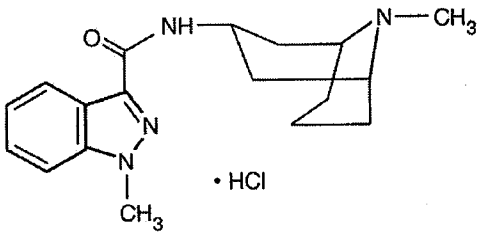
/s/

Gary DellaZanna
7/28/04 10:28:35 AM
MEDICAL OFFICER

Ruyi He
7/28/04 11:16:07 AM
MEDICAL OFFICER

Granisetron



NDA:	20-239 /S-015
Chemical Name:	Granisetron HCl
Class:	5-HT_3-receptor antagonist
Date Received:	January 9, 2004
Applicant:	Roche Inc.
Documents Reviewed:	Applicant Correspondence January 9, 2004 Communication with Kathleen Uhl (Pregnancy Labeling) Communication with Jani Parinda (Pediatric Division)
Division Director:	Robert Justice M.D.
Acting Team Leader:	Ruyi He M.D.
Medical Officer:	Gary Della'Zanna D.O. M.Sc.
Project Manager:	Betsy Scroggs Ph.D

Benzyl Alcohol

Background:

Granisetron Injection was first approved in December 1993 for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric and adult patients. Granisetron Tablets were approved March 1995 to treat adult patients with CINV, and in July 1999 received approval for prevention of adult radiation-induced nausea and vomiting (RINV). In June 2001, Granisetron Oral Solution was approved for treatment of adult patients with CINV or RINV. In August 2002, granisetron injection was then approved for the prevention and treatment of postoperative nausea and vomiting (PONV).

Presently, intravenous granisetron is available in two formulations, a 1mg/1ml single dose vial, and a 4mg/4ml multi-dose vial. The *approved* 4mg/4ml multi-dose vial includes benzyl alcohol as a preservative. The Applicant proposes a formulation change to the 1mg/1ml single dose vial to be the same as the 4mg/4ml multi-dose vial. On November 14, 2003 the Agency issued an *approvable letter recommending* the original 1mg/1ml formulation be retained since the addition of benzyl alcohol to a single dose vial is unnecessary.

Medical Officer Comment:
The use benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. In other recently revised drug labels, the Agency's concerns about benzyl alcohol were addressed under the Warning Section of the label.

The FRAGMIN label includes the following Warning:

> The multiple-dose vial of FRAGMIN contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

The proposed ⟵ label (in draft) is less restrictive, with the following statement:

[

]

[

]

The off label use of granisetron during pregnancy needs to be strongly considered since5-HT_3-receptor antagonist are used to treat Hyperemesis Gravidum. This complication of pregnancy is not uncommon, occurring in approximately 1 in 300 pregnancies.

The present intravenous granisetron printed label does not differentiate between the 1mg/1ml single dose and a 4mg/4ml multi-dose vial, which contains benzyl alcohol. The present label does not include a warning about benzyl alcohol.

To maintain consistency in the label across the divisions, this topic was discussed with the pregnancy labeling committee and the pediatric division. Kathleen Uhl, a member of the pregnancy labeling committee, stated the committee does not have standard language regarding the use of drug products that contain benzyl alcohol in pregnant women.. Jani Parinda, a member of the Pediatric Division, forwarded recommendation for label revisions for all drug products containing benzyl alcohol (see Recommendation below).

Recommendations:

The Division should issue an approvable letter pending revisions to the label outlined below. The proposed formulation change of the 1mg/1ml vial to include benzyl alcohol should be allowed. However, the Applicant should be informed that the label will need to be revised to reflect the Agency's *present* concerns regarding the use of drug products containing benzyl alcohol in *neonates*. The Applicant may wish to reconsider discontinuing the present 1mg/1ml vial formulation, since this label would not require the warning. The Applicant may consider generating separate labels for the 1mg/1ml vial and 4mg/4ml multi-dose vial to avoid this warning in the 1mg/1ml vial formulation.

The pregnancy labeling committee does not have a specific position regarding benzyl alcohol during pregnancy. However, they do not recommend making the drug contraindicated in pregnancy. Since benzyl alcohol may cross the placenta, the label should reflect this information under the Pregnancy Section.

The following represents the Agency's current position regarding products containing benzyl alcohol and should be placed in the printed label for formulations of granisetron, which include benzyl alcohol.

Under PRECAUTIONS: Pediatric use subsection

"Benzyl alcohol, a component of this drug product, has been associated with serious adverse events and death, particularly in [redacted] The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the 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-birthweight 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."

Under DOSAGE AND ADMINISTRATION section

"NOTE: CONTAINS BENZYL ALCOHOL (See PRECAUTIONS)" as a prominent statement in the first paragraph

Under PREGNANCY Section

Benzyl alcohol may cross the placenta. Granisetron Injection preserved with benzyl alcohol should be used in pregnancy only if the benefit outweighs the potential risk.

Under HOW SUPPLIED section.

Include the statement "CONTAINS BENZYL ALCOHOL"

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/s/

Gary DellaZanna
2/9/04 11:34:17 AM
MEDICAL OFFICER

Ruyi He
2/9/04 04:07:08 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-239/S015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-239/SCF-015

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

Sponsor: **Hoffman-LaRoche**

Material Reviewed

Submission Date: April 20, 2004

Receipt Date: April 22, 2004

Background and Summary

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.

Supplement SCF-015, submitted December 22, 2003 provides for a change in formulation to the 1 mg/1 mL vial including the addition of benzyl alcohol. The April 20, 2004 resubmission of supplement SCF-015 provides for a complete response to our November 14, 2003 action letter as well as a response to our March 29, 2004 supplement request letter asking the firm to update the labeling with strengthened standard language for drug products containing benzyl alcohol.

Draft electronic labeling included in the submission (19apr2004) was compared to the currently approved labeling (NDA 20-239/S-008) and the differences are noted below.

Review

Package insert

1. The symbol "Rx only" was added.

   This change is acceptable.

2. The revision date was changed to "19apr2004."

   This change is acceptable.

3. In the DESCRIPTION SECTION, the following was deleted:

"Single Dose Vials
Each 1 mL of preservative free aqueous solution contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg and sodium chloride, 9 mg. The solution's pH ranges from 4.7 to 73.

Multi-Dose Vials"

and in its place, the following 2 sentences were added:

"Each 1 mL contains 1.12 mg granisetron hydrochloride equivalent to granisetron hydrochloride equivalent to gransisetron, 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."

This change is acceptable per the chemistry review dated May 24, 2004.

4. In the PRECAUTIONS SECTION, Pediatric Use subsection, the following was added:

"Benzyl alcohol may cross the placenta. Granisetron injection preserved with benzyl alcohol should be used in pregnancy only if the benefit outweighs the potential risk."

This change is acceptable per the medical review dated July 28, 2004.

5. In the PEDIATRIC USE SECTION, the following was added:

"Benzyl alcohol, a component of this drug product, 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 birthweight 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."

This change is acceptable per the medical review dated July 28, 2004 stating that the firm has revised the label to include standard language for drug products containing benzyl alcohol.

6. In the DOSAGE AND ADMINISTRATION SECTION, the following was added:

   "NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS)."

   This change is acceptable per the medical review.

7. The HOW SUPPLIED SECTION was changed to include the statement "CONTAINS BENZYL ALCOHOL" and now reads "KYTRIL Injection, 1 mg/mL (free base), is supplied in 1 mL Single-Use Vials and 4 mL Multi-Dose Vials. CONTAINS BENZYL ALCOHOL."

   This change is acceptable per the chemistry review.

8. The previous copyright dates have been updated to 1998-2004. The "Rx only" symbol is moved to the top of the first page.

   These are acceptable changes.

Conclusions

In the draft labeling submitted with SCF-015, changes to DESCRIPTION, PRECAUTIONS (Pregnancy subsection), PEDIATRIC USE, DOSAGE AND ADMINISTRATION, AND HOW SUPPLIED sections were proposed. These changes are acceptable per the chemistry review dated May 24, 2004 and the clinical review dated July 28, 2004, both recommending approval. Based on these recommendations, an action letter will be drafted.

{See appended electronic signature page}
Betsy Scroggs, Pharm. D.
Consumer Safety Officer

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/s/

Betsy Scroggs
8/16/04 06:10:14 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-049/S-015

Hoffman-La Roche Inc.
Attention: Kathleen Schostack, Ph.D.
Group Director, Drug Regulatory Affairs, CMC
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Schostack:

We acknowledge receipt on April 20, 2004 of your April 22, 2004 resubmission to your supplemental new drug application for Kytril® Injection providing for addition of benzyl alcohol to the 1 mg/1 mL vial size.

We also refer to our supplement request letter dated March 19, 2004 asking for changes in the labeling to provide more information regarding the use of benzyl alcohol in the Kytril® Injection product formulations.

This amendment constitutes a complete response to our November 14, 2003 action letter and additionally provides for the requested changes in labeling for Kytril® 1 mg/1 mL and 4 mg/4 mL Injection. The user fee goal date is August 22, 2004.

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
6/28/04 11:15:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-239

Hoffmann-LaRoche Inc.
Attention: Kathleen Schostack, Ph.D.
Group Director, Technical Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Schostack:

Please refer to your new drug application (NDA) for Kytril® (granisetron) Injection 4 mg/4 mL and 1 mg/1 mL.

We also refer to your supplement #015 providing for the addition of benzyl alcohol to the 1 mg/1 mL formulation dated July 11, 2003 and to our approvable letter dated November 14, 2003.

Also refer to your letter dated January 8, 2004 requesting a teleconference to clarify the exact concerns of the Agency.

A meeting (teleconference) may be premature, as had been discussed with Ms. Sarah Orris, Program Manager. However, in consideration of your request, we have completed review of your January 8, 2004 submission and have the following comments and requests.

We have reviewed your product labeling and would like to provide the following options:

Option #1: The change in formulation for the addition of benzyl alcohol to the 1 mg/1 mL single-dose vial is approvable. You should submit revised labeling as requested below.

Option #2: Retain the original formulation for the 1 mg/1 mL vial without benzyl alcohol and submit revised labeling to include the benzyl alcohol statements for the 4 mg/4 mL vial as requested below.

To reflect our present concerns regarding the use of drug products containing benzyl alcohol in neonates, we request that you make the following changes to the PRECAUTIONS: Pediatric Use and Pregnancy subsections, to the DOSAGE AND ADMINISTRATION section, and to the HOW SUPPLIED section to provide information regarding the use of benzyl alcohol in these product formulations so as to furnish adequate information for the safe and effective use of the drug.

Under the PRECAUTIONS: Pediatric Use Subsection add the following paragraph.

> "Benzyl alcohol, a component of this drug product, has been associated with serious adverse events and death, particularly in [redacted] 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-birthweight 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."

Under the PRECAUTIONS, Pregnancy Subsection add the following paragraph.

> "Benzyl alcohol may cross the placenta. Granisetron Injection preserved with benzyl alcohol should be used in pregnancy only if the benefit outweighs the potential risk."

Under the DOSAGE AND ADMINISTRATION section, add the following sentences as a prominent statement in the first paragraph.

> "NOTE: CONTAINS BENZYL ALCOHOL (See PRECAUTIONS)."

Under HOW SUPPLIED section, include the following statement.

> "CONTAINS BENZYL ALCOHOL."

Submit draft labeling as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made as well as in electronic format with the current, proposed, and annotated versions in PDF and Word accompanied by a well-organized table of contents.

If you still feel that you still require a meeting or teleconference with the Agency, you should refer to the guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), which describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm

If you have any questions, call Dr. Betsy Scroggs, Consumer Safety Officer, at 301-827-1250.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & 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/

Robert Justice
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