CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-305/S010
21-238/S005

Trade Name: Kytril Tablets
Kytril Oral Solutions

Generic Name: (granisetron hydrochloride)

Sponsor: Hoffman-LaRoche Inc.

Approval Date: November 23, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-305/S010

21-238/S005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-305/S010

NDA 21-238/S005

APPROVAL LETTER

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

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 applications dated September 1, 2004, received September 8, 2004, submitted section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril® (granisetron hydrochloride) Tablets (NDA 20-305) and Kytril® (granisetron hydrochloride) Oral Solution.

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

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

These supplemental new drug applications provide for revisions to the PRECAUTIONS section, Drug Interactions subsection.

We completed our review of these applications, as amended. These applications are 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 labeling text for the Package Insert and submitted Package Insert (submitted May 20, 2005).

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 these submissions "**FPL for approved supplement NDA 20-305/S-010 and NDA 21-238/S-005**." Approval of these submissions 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 IIICenter 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 11:04:56 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-305/S010

NDA 21-238/S005

APPROVABLE LETTER

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

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

Dear Mr. Corrado:

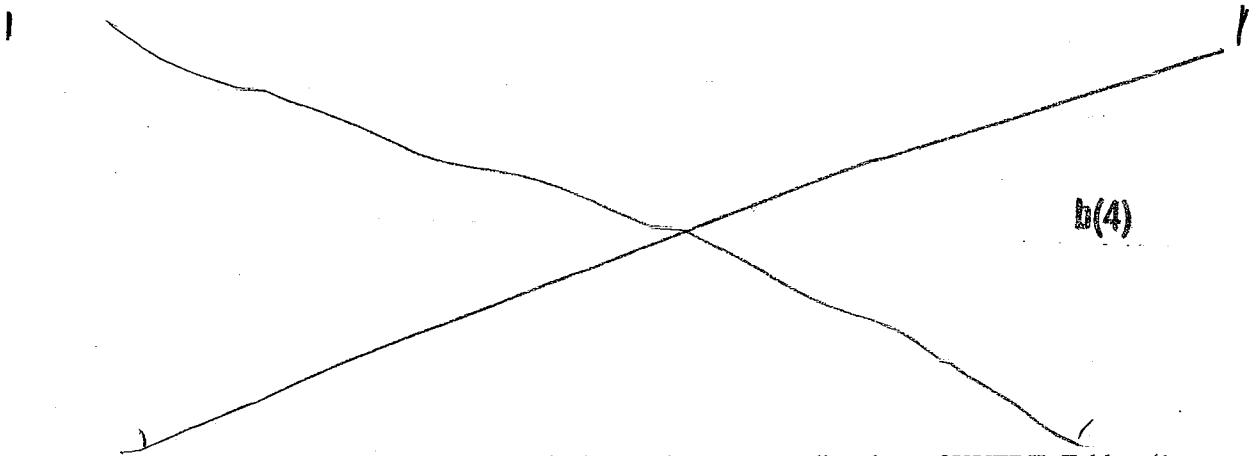
Please refer to your supplemental new drug applications dated September 1, 2004, received September 8, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril® (granisetron hydrochloride) Tablets and Kytril® (granisetron hydrochloride) Oral Solution.

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

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

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

Pharmacokinetics



~~A 2 mg dose of KYTRIL Oral Solution is bioequivalent to the corresponding dose of KYTRIL Tablets (1 mg x 2) and may be used interchangeably.~~

Absorption

When KYTRIL Tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

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 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

Subpopulations

Gender

The effects of gender on the pharmacokinetics of KYTRIL Tablets have not been studied. However, after intravenous infusion of KYTRIL, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous KYTRIL:
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.
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 with intravenous KYTRIL 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 dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.
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.

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, 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 b(4) 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]

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 these application(s), notify us of your intent to file an amendment(s), 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 12:26:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-305/S010

NDA 21-238/S005

LABELING

KYTRIL®

(granisetron hydrochloride)

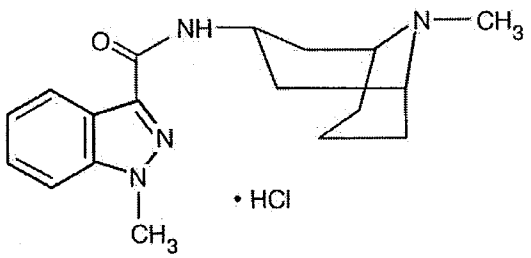
TABLETS

ORAL SOLUTION

R_x only

DESCRIPTION

KYTRIL Tablets and KYTRIL Oral Solution contain granisetron hydrochloride, 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.

Tablets for Oral Administration

Each white, triangular, biconvex, film-coated KYTRIL Tablet contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg. Inactive ingredients are: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Oral Solution

Each 10 mL of clear, orange-colored, orange-flavored KYTRIL Oral Solution contains 2.24 mg of granisetron hydrochloride equivalent to 2 mg granisetron. Inactive ingredients: citric acid anhydrous, FD&C Yellow No. 6, orange flavor, purified water, sodium benzoate, and sorbitol.

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 that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT$_3$ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT$_3$ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

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

Following single and multiple oral doses, KYTRIL Tablets slowed colonic transit in normal volunteers. However, KYTRIL had no effect on oro-cecal transit time in normal volunteers when given as a single intravenous (IV) infusion of 50 mcg/kg or 200 mcg/kg.

Pharmacokinetics

In healthy volunteers and adult cancer patients undergoing chemotherapy, administration of KYTRIL Tablets produced mean pharmacokinetic data shown in **Table 1.**

Table 1 Pharmacokinetic Parameters (Median [range]) Following KYTRIL Tablets (granisetron hydrochloride)

	Peak Plasma Concentration (ng/mL)	Terminal Phase Plasma Half-Life (h)	Volume of Distribution (L/kg)	Total Clearance (L/h/kg)
Cancer Patients 1 mg bid, 7 days (n=27)	5.99 [0.63 to 30.9]	N.D.[1]	N.D.	0.52 [0.09 to 7.37]
Volunteers single 1 mg dose (n=39)	3.63 [0.27 to 9.14]	6.23 [0.96 to 19.9]	3.94 [1.89 to 39.4]	0.41 [0.11 to 24.6]

[1] Not determined after oral administration; following a single intravenous dose of 40 mcg/kg, terminal phase half-life was determined to be 8.95 hours.

N.D. Not determined.

A 2 mg dose of KYTRIL Oral Solution is bioequivalent to the corresponding dose of KYTRIL Tablets (1 mg x 2) and may be used interchangeably.

Absorption

When KYTRIL Tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

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 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

Subpopulations

Gender

The effects of gender on the pharmacokinetics of KYTRIL Tablets have not been studied. However, after intravenous infusion of KYTRIL, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous KYTRIL:

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.

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 with intravenous KYTRIL 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 dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.

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.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting

KYTRIL Tablets prevent nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, as shown by 24-hour efficacy data from studies using both moderately- and highly-emetogenic chemotherapy.

Moderately Emetogenic Chemotherapy

The first trial compared KYTRIL Tablets doses of 0.25 mg to 2 mg bid, in 930 cancer patients receiving, principally, cyclophosphamide, carboplatin, and cisplatin (20 mg/m^2 to 50 mg/m^2). Efficacy was based on complete response (ie, no vomiting, no moderate or severe nausea, no rescue medication), no vomiting, and no nausea. **Table 2** summarizes the results of this study.

Table 2 Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

	Percentages of Patients KYTRIL Tablet Dose			
Efficacy Measures	**0.25 mg bid (n=229) %**	**0.5 mg bid (n=235) %**	**1 mg bid (n=233) %**	**2 mg bid (n=233) %**
Complete Response[2]	61	70*	81*†	72*
No Vomiting	66	77*	88*	79*
No Nausea	48	57	63*	54

1 Chemotherapy included oral and injectable cyclophosphamide, carboplatin, cisplatin (20 mg/m^2 to 50 mg/m^2), dacarbazine, doxorubicin, epirubicin.

2 No vomiting, no moderate or severe nausea, no rescue medication.

*Statistically significant (P<0.01) vs. 0.25 mg bid.

†Statistically significant (P<0.01) vs. 0.5 mg bid.

Results from a second double-blind, randomized trial evaluating KYTRIL Tablets 2 mg qd and KYTRIL Tablets 1 mg bid were compared to prochlorperazine 10 mg bid derived from a historical control. At 24 hours, there was no statistically significant difference in efficacy between the two KYTRIL Tablet regimens. Both regimens were statistically superior to the prochlorperazine control regimen (see **Table 3**).

Table 3 Prevention of Nausea and Vomiting 24 Hours Post-Chemotherapy[1]

	Percentages of Patients		
Efficacy Measures	**KYTRIL Tablets 1 mg bid (n = 354) %**	**KYTRIL Tablets 2 mg qd (n = 343) %**	**Prochlorperazine[2] 10 mg bid (n=111) %**
Complete Response[3]	69*	64*	41
No Vomiting	82*	77*	48
No Nausea	51*	53*	35
Total Control[4]	51*	50*	33

1 Moderately emetogenic chemotherapeutic agents included cisplatin (20 mg/m^2 to 50 mg/m^2), oral and intravenous cyclophosphamide, carboplatin, dacarbazine, doxorubicin.

[2] Historical control from a previous double-blind KYTRIL trial.
[3] No vomiting, no moderate or severe nausea, no rescue medication.
[4] No vomiting, no nausea, no rescue medication.
*Statistically significant (P<0.05) vs. prochlorperazine historical control.

Results from a KYTRIL Tablets 2 mg qd alone treatment arm in a third double-blind, randomized trial, were compared to prochlorperazine (PCPZ), 10 mg bid, derived from a historical control. The 24-hour results for KYTRIL Tablets 2 mg qd were statistically superior to PCPZ for all efficacy parameters: complete response (58%), no vomiting (79%), no nausea (51%), total control (49%). The PCPZ rates are shown in **Table 3**.

Cisplatin-Based Chemotherapy

The first double-blind trial compared KYTRIL Tablets 1 mg bid, relative to placebo (historical control), in 119 cancer patients receiving high-dose cisplatin (mean dose 80 mg/m^2). At 24 hours, KYTRIL Tablets 1 mg bid was significantly (P<0.001) superior to placebo (historical control) in all efficacy parameters: complete response (52%), no vomiting (56%) and no nausea (45%). The placebo rates were 7%, 14%, and 7%, respectively, for the three efficacy parameters.

Results from a KYTRIL Tablets 2 mg qd alone treatment arm in a second double-blind, randomized trial, were compared to both KYTRIL Tablets 1 mg bid and placebo historical controls. The 24-hour results for KYTRIL Tablets 2 mg qd were: complete response (44%), no vomiting (58%), no nausea (46%), total control (40%). The efficacy of KYTRIL Tablets 2 mg qd was comparable to KYTRIL Tablets 1 mg bid and statistically superior to placebo. The placebo rates were 7%, 14%, 7%, and 7%, respectively, for the four parameters.

No controlled study comparing granisetron injection with the oral formulation to prevent chemotherapy-induced nausea and vomiting has been performed.

Radiation-Induced Nausea and Vomiting

Total Body Irradiation

In a double-blind randomized study, 18 patients receiving KYTRIL Tablets, 2 mg daily, experienced significantly greater antiemetic protection compared to patients in a historical negative control group who received conventional (non-5-HT_3 antagonist) antiemetics. Total body irradiation consisted of 11 fractions of 120 cGy administered over 4 days, with three fractions on each of the first 3 days, and two fractions on the fourth day. KYTRIL Tablets were given one hour before the first radiation fraction of each day.

Twenty-two percent (22%) of patients treated with KYTRIL Tablets did not experience vomiting or receive rescue antiemetics over the entire 4-day dosing period, compared to 0% of patients in the historical negative control group (P<0.01).

In addition, patients who received KYTRIL Tablets also experienced significantly fewer emetic episodes during the first day of radiation and over the 4-day treatment period, compared to patients in the historical negative control group. The median time to the first emetic episode was 36 hours for patients who received KYTRIL Tablets.

Fractionated Abdominal Radiation

The efficacy of KYTRIL Tablets, 2 mg daily, was evaluated in a double-blind, placebo-controlled randomized trial of 260 patients. KYTRIL Tablets were given 1 hour before radiation, composed of up to 20 daily fractions of 180 to 300 cGy each. The exceptions were patients with seminoma or those receiving whole abdomen irradiation who initially received 150 cGy per fraction. Radiation was administered to the upper abdomen with a field size of at least 100 cm^2.

The proportion of patients without emesis and those without nausea for KYTRIL Tablets, compared to placebo, was statistically significant ($P<0.0001$) at 24 hours after radiation, irrespective of the radiation dose. KYTRIL was superior to placebo in patients receiving up to 10 daily fractions of radiation, but was not superior to placebo in patients receiving 20 fractions.

Patients treated with KYTRIL Tablets (n=134) had a significantly longer time to the first episode of vomiting (35 days vs. 9 days, $P<0.001$) relative to those patients who received placebo (n=126), and a significantly longer time to the first episode of nausea (11 days vs. 1 day, $P<0.001$). KYTRIL provided significantly greater protection from nausea and vomiting than placebo.

INDICATIONS AND USAGE

KYTRIL (granisetron hydrochloride) is indicated for the prevention of:

- Nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
- Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

CONTRAINDICATIONS

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

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 4, 20, and 101 times the recommended clinical dose (1.48 mg/m^2, oral) 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, 20 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, 101 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, 4 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 20 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, 405 times the recommended human dose based on body surface area) produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24-month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

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

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

Granisetron at oral doses up to 100 mg/kg/day (600 mg/m^2/day, 405 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 oral doses up to 125 mg/kg/day (750 mg/m^2/day, 507 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 32 mg/kg/day (378 mg/m^2/day, 255 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

During clinical trials, 325 patients 65 years of age or older received KYTRIL Tablets; 298 were 65 to 74 years of age, and 27 were 75 years of age or older. Efficacy and safety were maintained with increasing age.

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting

Over 3700 patients have received KYTRIL Tablets in clinical trials with emetogenic cancer therapies consisting primarily of cyclophosphamide or cisplatin regimens.

In patients receiving KYTRIL Tablets 1 mg bid for 1, 7 or 14 days, or 2 mg qd for 1 day, adverse experiences reported in more than 5% of the patients with comparator and placebo incidences are listed in **Table 4**.

Table 4 Principal Adverse Events in Clinical Trials

	Percent of Patients With Event			
	KYTRIL[1] Tablets 1 mg bid (n=978)	KYTRIL[1] Tablets 2 mg qd (n=1450)	Comparator[2] (n=599)	Placebo (n=185)
Headache[3]	21%	20%	13%	12%
Constipation	18%	14%	16%	8%
Asthenia	14%	18%	10%	4%
Diarrhea	8%	9%	10%	4%
Abdominal pain	6%	4%	6%	3%
Dyspepsia	4%	6%	5%	4%

[1] Adverse events were recorded for 7 days when KYTRIL Tablets were given on a single day and for up to 28 days when KYTRIL Tablets were administered for 7 or 14 days.

[2] Metoclopramide/dexamethasone; phenothiazines/dexamethasone; dexamethasone alone; prochlorperazine.

[3] Usually mild to moderate in severity.

Other adverse events reported in clinical trials were:

Gastrointestinal: In single-day dosing studies in which adverse events were collected for 7 days, nausea (20%) and vomiting (12%) were recorded as adverse events after the 24-hour efficacy assessment period.

Hepatic: In comparative trials, elevation of AST and ALT (>2 times the upper limit of normal) following the administration of KYTRIL Tablets occurred in 5% and 6% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2%; ALT: 9%).

Cardiovascular: Hypertension (1%); hypotension, angina pectoris, atrial fibrillation, and syncope have been observed rarely.

Central Nervous System: Dizziness (5%), insomnia (5%), anxiety (2%), somnolence (1%). One case compatible with, but not diagnostic of, extrapyramidal symptoms has been reported in a patient treated with KYTRIL Tablets.

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

Other: Fever (5%). Events often associated with chemotherapy also have been reported: leukopenia (9%), decreased appetite (6%), anemia (4%), alopecia (3%), thrombocytopenia (2%).

Over 5000 patients have received injectable KYTRIL in clinical trials.

Table 5 gives the comparative frequencies of the five commonly reported adverse events (≥3%) in patients receiving KYTRIL Injection, 40 mcg/kg, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following KYTRIL Injection administration.

Table 5 Principal Adverse Events in Clinical Trials — Single-Day Chemotherapy

	Percent of Patients with Event	
	KYTRIL Injection[1] 40 mcg/kg (n=1268)	**Comparator[2] (n=422)**
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

[1] Adverse events were generally recorded over 7 days post-KYTRIL Injection administration.

[2] Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

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.

Radiation-Induced Nausea and Vomiting

In controlled clinical trials, the adverse events reported by patients receiving KYTRIL Tablets and concurrent radiation were similar to those reported by patients receiving KYTRIL Tablets prior to chemotherapy. The most frequently reported adverse events were diarrhea, asthenia, and constipation. Headache, however, was less prevalent in this patient population.

OVERDOSAGE

There is no specific treatment for granisetron hydrochloride 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

Emetogenic Chemotherapy

The recommended adult dosage of oral KYTRIL (granisetron hydrochloride) is 2 mg once daily or 1 mg twice daily. In the 2 mg once-daily regimen, two 1 mg tablets or 10 mL of KYTRIL Oral Solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are given up to 1 hour before chemotherapy. In the 1 mg twice-daily regimen, the first 1 mg tablet or one teaspoonful (5 mL) of KYTRIL Oral Solution is given up to 1 hour before chemotherapy, and the second tablet or second teaspoonful (5 mL) of KYTRIL Oral Solution, 12 hours after the first. Either regimen is administered only on the day(s) chemotherapy is given. Continued treatment, while not on chemotherapy, has not been found to be useful.

Use in the Elderly, Pediatric Patients, Renal Failure Patients or Hepatically Impaired Patients

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

Radiation (Either Total Body Irradiation or Fractionated Abdominal Radiation)

The recommended adult dosage of oral KYTRIL is 2 mg once daily. Two 1 mg tablets or 10 mL of KYTRIL Oral Solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are taken within 1 hour of radiation.

Pediatric Use

There is no experience with oral KYTRIL in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Use in the Elderly

No dosage adjustment is recommended.

HOW SUPPLIED

Tablets

White, triangular, biconvex, film-coated tablets; tablets are debossed K1 on one face.

1 mg Unit of Use 2's: NDC 0004-0241-33

1 mg Single Unit Package 20's: NDC 0004-0241-26 (intended for institutional use only)

Storage

Store between 15° and 30°C (59° and 86°F). Keep container closed tightly. Protect from light.

Oral Solution

Clear, orange-colored, orange-flavored, 2 mg/10 mL, in 30 mL amber glass bottles with child-resistant closures: NDC 0004-0237-09

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep bottle closed tightly and stored in an upright position. Protect from light.

Distributed by:

Pharmaceuticals

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

XXXXXXXX

Revised: Month Year

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-305/S010

NDA 21-238/S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-305/SLR-010 — LETTER DATE: 09/01/04
Granisetron HCl, Oral Tablet (1 mg)

NDA: 21-238/SLR-005 — LETTER DATE: 09/01/04
Granisetron HCl, Oral Solution (2 mg/10 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) oral tablet (NDA 20-305) was approved by the Agency on 05/16/95 and Kytril oral solution, 2 mg/10 mL (NDA 21-238), was approved on 06/27/01. They are indicated for **1)** the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin and **2)** the prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

On 09/01/04, Roche submitted labeling supplements SLR-010 and SLR-005 to NDA's 20-305 and 21-238, respectively. The two products have a common package insert and as such identical information has been submitted to both supplements. Changes to the Drug Interactions subsection of the Precautions section in the approved package insert are proposed based on information from six reports. The proposed changes are shown below:

I. Under PRECAUTIONS Section;

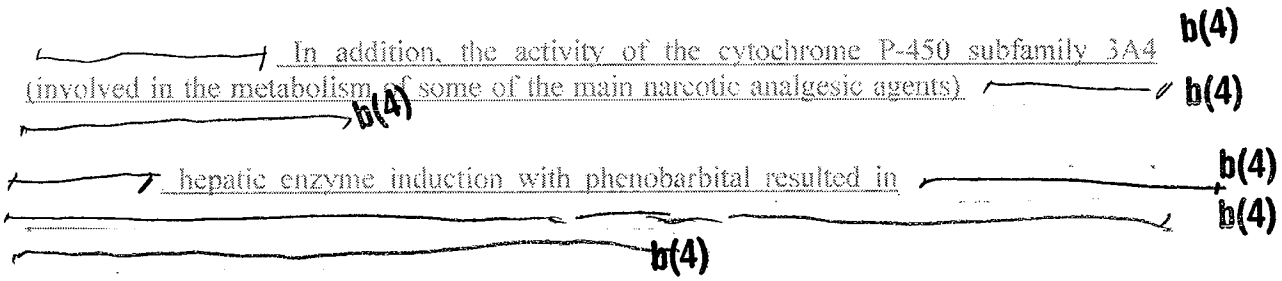
PRECAUTIONS

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.

II. 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.

b(4)



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, 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 presence 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 of 4 μg/kg of granisetron given as a 5-minute infusion on Days 1 and 15 was studied in sixteen adult healthy male volunteers before and after potential liver induction caused by repeated oral dosing of 100 mg dose of phenobarbital 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, 13% higher volume of distribution, and 10% slightly shorter half-life 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)

1. After the Table 1 in the Pharmacokinetics subsection under CLINICAL PHARMACOLOGY Section, the pharmacokinetics information should be revised:

Absorption

When KYTRIL Tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

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 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

Subpopulations

Gender

The effects of gender on the pharmacokinetics of KYTRIL Tablets have not been studied. However, after intravenous infusion of KYTRIL, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous KYTRIL:

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.

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 with intravenous KYTRIL 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 dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.

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.

2. 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] b(4) b(4) [redacted] 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]

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's SLR-010 to NDA 20-305 and SLR-005 to NDA 21-238 are acceptable provided that a satisfactory agreement can be reached between the Agency and the Sponsor. For consistency with Kytril Injection (NDA 20-239), the Pharmacokinetics subsection of the labeling for tablet and oral solution should be modified. 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 20-305 (SLR-010) for Kytril (Granisetron HCl; 1 mg) Tablets

NDA 21-238 (SLR-005) for Kytril (Granisetron HCl; 2 mg/10 mL) Oral Solution

Appendix

Sponsor Proposed Annotated Labeling (09/01/04)

13 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- 20-305/S020
21-238/S005

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 10:16:25 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/4/05 12:23:23 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-305/S010

NDA 21-238/S005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY HEALTH PROJECT MANAGER REVIEW

Application Numbers	Name of Drugs
NDA 20-305/SLR-010/AL	Kytril® (granisetron hydrochloride) Tablets
NDA 21-238/SLR-005/AL	Kytril® (granisetron hydrochloride) Oral Solution

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) Tablets, NDA 20-305, approved March 16, 1995 and Kytril® (granisetron hydrochloride) Oral Solution, NDA 21-238, approved June 27, 2001, are indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin, and nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation. Please note that NDA 20-305 and NDA 21-238 share the same label. In addition, NDA 21-238, Kytril® Oral Solution is bioequivalent to NDA 20-305, Kytril® Tablets and is noted since this is an approved statement in the original NDA 21-283 Package Insert (PI) approved June 27, 2001.

Supplement NDA 20-305/SE2-001 approved October 6, 1997 provided for a new dosing regimen (2 mg daily instead of 1 mg twice daily).

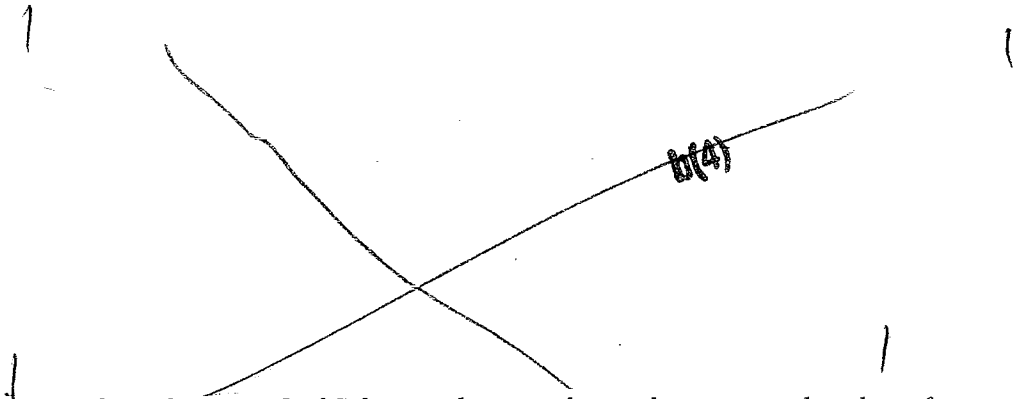
Supplement NDA 20-305/SE1-004, approved July 27, 1999 provided for the treatment of radiation induced nausea and vomiting (RINV).

Supplements to NDA 20-305/SLR-010 and NDA 21-238/SLR-005 submitted September 1, 2004 provided for changes to the **PRECAUTIONS**, Drug Interactions sub-section of their common Package Insert (PI).

The March 4, 2005 Biopharmaceutics review recommended the following changes to the firm's proposed PI which are denoted by underlined and ~~struck through~~ text:

A. Pharmacokinetics

[redacted] b(4)



~~*A 2 mg dose of KYTRIL Oral Solution is bioequivalent to the corresponding dose of KYTRIL Tablets (1 mg x 2) and may be used interchangeably.*~~

Absorption

When KYTRIL Tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

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 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

Subpopulations

Gender

The effects of gender on the pharmacokinetics of KYTRIL Tablets have not been studied. However, after intravenous infusion of KYTRIL, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous KYTRIL:

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.*

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 with intravenous KYTRIL 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 dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.*

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.*

B. 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, 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) [redacted] b(4)

[redacted] *[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)

[redacted] *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~~ is not known.[6]

2. *In addition, the Clinical Reviewer verbally communicated the following revision on March 3, 2005 and added the following to the* ***Drug Interactions*** *sub-section which is noted by* ~~*struck-through*~~ *text below:*

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

The March 8, 2005 Regulatory Project Manager (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, 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."

Review

The proposed draft PI, submitted May 20, 2005 and identified (XXXXXXXX, Revised: MonthYear, S-010 and S-005) was compared to the currently approved PI identified as (27898474, NDA 21-238, Revised: June 2001) approved June 27, 2001.

All proposed changes were indicated in the sponsor's annotated proposed PI.

1. In the CLINICAL PHARMACOLOGY SECTION, Pharmacokinetics subsection, the sponsor has reinserted the following:

   "A 2 mg dose of KYTRIL Oral Solution is bioequivalent to the corresponding dose of KYTRIL Tablets (1 mg x 2) and may be used interchangeably."

   Comment: In the Biopharmaceutics reviewer's "NAI" Document File System (DFS) entry dated November 18, 2005, he comments that the Biopharmaceutics review team agrees with the reinsertion of the above sentence. The change is acceptable.

2. Other Revisions:

   Comment: The sponsor has made all requested changes with minor editorial revisions that do not change the context of the label.

Conclusions

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

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

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: BHS 11-17-2005
Revised/Initialed:JD 11-21-2005
Finalized: BHS/11-21-2005
Filename: C:\CDERAPPS\Data\My Documents\Kytril SLRs\Oral\FINAL bhs Kytri_PM_Labeling Review_Oral formulations.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/

Betsy Scroggs
11/21/2005 04:10:51 PM
CSO

Julieann DuBeau
11/21/2005 04:30:46 PM
CSO

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY HEALTH PROJECT MANAGER REVIEW

Application Number: NDA 20-305/SLR-010 and NDA 21-238/SLR-005

Name of Drug: Kytril® (granisetron hydrochloride) Tablets and Kytril® (granisetron hydrochloride) Oral Solution

Sponsor: Hoffman-LaRoche

Material Reviewed

Submission Date(s): September 1, 2004

Receipt Date(s): September 8, 2004

Background and Summary Description

KYTRIL (granisetron hydrochloride) Tablets and Kytril® (granisetron hydrochloride) Oral Solution are currently indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin, and nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation. Please note that NDAs 20-305 and 21-238 share the same label.

The currently proposed labels, NDA 20-305/SLR-010 and NDA 21-238/SLR-005, propose changes to the **PRECAUTIONS** section and **Drug Interactions** sub- section of the package insert.

Review

1. The proposed labeling (XXXXXXXX, S-010 and S-005, dated: 09/01/04, received: 09/08/04) was compared electronically to the currently approved labeling (27898474, NDA 21-238, dated: 08/30/00, received: 08/31/00, approved: 06/27/01). All proposed changes were indicated in the sponsor's annotated proposed label. The *proposed changes* were as follows, and are noted by *underline*:

   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 drugmetabolizing 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 drugmetabolizing 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.* *[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* *hepatic enzyme induction with phenobarbital resulted in* *KYTRIL.[2] The clinical significance of these changes is not known.*

b(4) b(4) b(4) b(4) b(4) 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 **Pharmacokinetics** sub-section of the **CLINICAL PHARMACOLOGY** Section, and **Drug Interactions** sub-section in his 03/04/05 review which are denoted by underlined and ~~struck-through~~ text:

A. Pharmacokinetics

b(4)

~~*A 2 mg dose of KYTRIL Oral Solution is bioequivalent to the corresponding dose of KYTRIL Tablets (1 mg x 2) and may be used interchangeably.*~~

Absorption

When KYTRIL Tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

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 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

Subpopulations

Gender

The effects of gender on the pharmacokinetics of KYTRIL Tablets have not been studied. However, after intravenous infusion of KYTRIL, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of intravenous KYTRIL:
***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.*
***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 with intravenous KYTRIL 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 dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.*
***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.*

B. 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, 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]*

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 03/03/05 that he agreed with Dr. Chen's above recommendations and also recommended the following additional change in the **Drug Interactions** sub-section 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

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/s/

Melissa Furness
3/8/05 11:05:56 AM
CSO

Julieann DuBeau
3/8/05 11:09:29 AM
CSO
Signing for Brian Strongin, Co-CPMS.

Gary DellaZanna
3/8/05 11:10:18 AM
MEDICAL OFFICER

Ruyi He
3/8/05 11:16:44 AM
MEDICAL OFFICER
Signing for Hugo Gallo-Torres

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

b(4)

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
8/11/05 01:27:22 PM

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
[redacted]	[redacted]	[redacted]
Kytril® (granisetron hydrochloride) Tablets, 1 mg	20-305	010

b(4)

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
10/27/04 04:26:04 PM