DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-239/S-016 & S-017

Hoffman-La Roche Inc.
Attention: Christine Hoogmoed
Senior C.M.C. Associate
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Hoogmoed:

Please refer to your supplemental new drug applications dated May 17, 2004, received May 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril® Injection.

These supplemental applications provide for the following:

1. S-016 provides for a change in formulation to add a 0.1 mg/1 mL single-use vial and

2. S-017 provides for the addition of an alternate secondary packaging site in Kaiseraugst, Switzerland for the 1 mg/1 mL vial and 4 mg/4 mL vial.

We completed our review of these applications. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the following requested minor editorial revisions listed below in double-underline:

1. The submitted draft vial label (27898742-L 5/13/04) is missing the stated volume "1" for the vial and should read as follows:

   "0.1 mg/1 mL
   Single-Use Vial"

   and be located above the drug name "Kytril®".

2. The submitted draft carton label for 1 vial (27898741-C 5/13/04) is missing the stated volume "1" for the vial size in two locations contained in the carton and should read as follows:

   "0.1 mg/1 mL"

   and be located in the middle of the front panel below the established name as well as

   "1 x 0.1 mg/1 mL"
   Single-Use Vial"

   and be located at the bottom of the front panel below the Rxonly text respectively.

3. The submitted draft carton label for 5 vials (2789XXX) is missing the stated volume "1" for the vial size in 4 locations (includes the photograph of the Kytril® vial) contained in the carton and should read as follows:

   "0.1 mg/1 mL"

   and be located in the middle of the front panel below the established name and as

   "5 x 0.1 mg/1 mL Single-Use Vials"

   and be located at the bottom of the front panel below the Rxonly text, as well as the changes in #1 above to address the changes needed to include the 1 mL vial photograph located on the right side of the front panel.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the package insert (May2004) submitted May 17, 2004, container label (27898742-L) submitted May 17, 2004, carton for 1 vial (277898741-C) submitted May 17, 2004 and carton for 5 vials (2789XXXX) submitted May 17, 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-016." 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}

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

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/s/

Joyce Korvick
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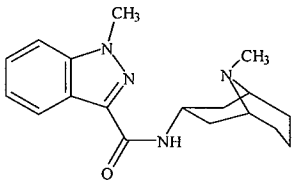
CHEMIST'S REVIEW 3	1. Organization: HFD-180	2. NDA Number: 20-239	
3. Name and Address of Applicant (City & State): Hoffmann-La Roche Inc. 340 Kingland Street Nutley, NJ 07110-1199		4. AF Number:	
		Supplement(s)	
6. Name of Drug: Kytril	7. Nonproprietary Name: Granisetron Hydrochloride	Number(s) SCF-016 SCM-017	Date(s) May 17, 2003
8. Supplement Provides for • New, low-dosage strength 0.1 mg/1ml of Kytril injection • Alternative secondary packaging site for the other two dosing strengths		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: 0.1 mg/mL		
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/JKorvick** **HFD-180/ZGe** **HFD-180/AAlhakim** **R/D init by:LZhou**			
18. Conclusions and Recommendations: This supplement may be approved based on CMC point of view, pending Clinical and Biopharm concurrence.			
19.Reviewer			
Name: Zhengfang Ge	Signature	Date Completed: Aug 25, 2004	

4 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
S016

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/s/

Zhengfang Ge
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CHEMIST

Ali Al-Hakim
8/30/04 02:43:24 PM
CHEMIST
Ali Al-Hakim for Liang Zhou

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-239/SCF-016

Name of Drug: **Kytril® (granisetron) 0.1 mg/1 mL vial**

Sponsor: **Hoffman-LaRoche**

Material Reviewed

Submission Date: May 17, 2004

Receipt Date: May 18, 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.

Supplement SCF-016, submitted May 17, 2004 provides for a new, low-dosage strength (0.1 mg/1 mL).

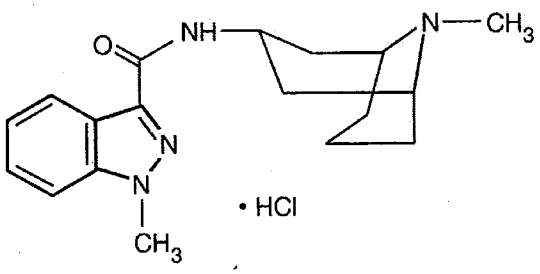
Review

Package insert

Draft paper labeling included in this submission incorporated the pending changes for S-015 (highlighted in yellow, 19apr2004) approved August 20, 2004 and pending changes for S-016 (highlighted in green, xxmay/2004). The following differences, as indicated by underline and bubbled comments were noted:

DESCRIPTION

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



granisetron hydrochloride

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

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

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

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

Pregnancy

Teratogenic Effects. *Pregnancy Category B.*

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

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

Pediatric Use

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

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

DOSAGE AND ADMINISTRATION

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

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)

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

NDC 0004-0242-09 (package of 1 Single-Dose Vial)

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

Distributed by:

Roche Pharmaceuticals

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

XXXXXXXX

Revised: Month Year

Comments: These are acceptable changes per the Chemistry review dated August 30, 2004.
Biopharmaceutics and Clinical reviews were not completed as the respective reviewers, Suresh Doddapaneni and Gary Della'Zanna indicated there was no action required from them (NR).

Container label

The proposed draft container label (27898742-L, dated: May 17, 2004 received: May 18, 2004) was compared to the container label for Kytril Injection, 1 mg /1 mL submitted in Y-010 (27897424-0201-L, dated February 18, 2004, received February 19, 2004).

Carton for 1 vial and Carton for 5 vials

The proposed draft carton for 1 vial (27899741-C, dated: May 17, 2004 received May 18, 2004) and draft carton for 5 vials (2789XXX) were compared to the carton for (Kytril 1 mg/1 mL Injection) submitted in Y-010 (27897426-0201, dated February 18, 2004, received February 19, 2004).

Carton for 5 vials missing 1 mL

Comments: The sponsor has made some formatting changes for the carton label, carton for 1 vial and carton for 5 vials.

- **For the container label, the following are missing: NDA number, Lot/Exp area, "For I.V. use only, and 1 mL. These missing elements should be added to the container label.**
- **The carton for 1 vial is acceptable.**
- **The carton for 5 vials is missing the 1 mL and should be added.**

Recommendations:

In the draft labeling submitted with SCF-015, changes were proposed to the following labeling: package insert, addition of a vial label, addition of a container label for 1 vial, and addition of a container label for 5 vials. Within the package insert, specific changes to DESCRIPTION, Pregnancy, Pediatric Use, DOSAGE AND ADMINISTRATION and HOW SUPPLIED sections were proposed.

These were acceptable changes per the Chemistry review dated August 30, 2004 recommending approval.

The following recommendations should be conveyed to the sponsor:

- For the container label, the following are missing: NDA number, Lot/Exp area, "For I.V. use only, and 1 mL. These missing elements should be added to the container label.
- The carton for 5 vials is missing the 1 mL and should be added.

Conclusions:

An action letter recommending approval with recommendations will be drafted and sent to the sponsor.

{See appended electronic signature page}

Betsy Scroggs, Pharm. D.
Consumer Safety Officer

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/s/

Betsy Scroggs
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CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-039/S-016 & S-017

Hoffman-La Roche Inc.
Attention: Christine Hoogmoed
Senior C.M.C. Associate
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Hoogmoed:

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

Name of Drug Product:	Kytril® Injection
NDA Number:	20-049
Supplement numbers:	016 & 017
Date of supplements:	May 17, 2004
Date of receipt:	May 18, 2004

As noted above, the submission has been administratively split into two supplements to clearly delineate and track the two requested changes.

These supplemental applications provide for the following:

b(4)

1. S-016 provides for a change in formulation to add a / - / mL single-use vial and

2. S-017 provides for the addition of an alternate secondary packaging site in Kaiseraugst, Switzerland for the 1 mg/1 mL vial and 4 mg/4 mL vial.

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file theses applications on July 17, 2004 in accordance with 21 CFR 314.101(a). If these applications are filed, the user fee goal date will be September 18, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service or Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Gastrointestional and Coagulation Drug Products
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Request: Please provide electronic copies of your proposed package insert, currently approved package insert, and marked up version in PDF and Word in order to facilitate the review of S-016.

Please contact me if you have any questions by calling 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, HFD 180
Center for Drug Evaluation and Research

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/s/

Betsy Scroggs
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