CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-238

Administrative Documents

EXCLUSIVITY SUMMARY for NDA # 21-238 SUPPL # _____

Trade Name Kytril Generic Name granisetron oral sol'n
Applicant Name Hoffmann-La Roche Inc. HFD- 180

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X/ NO /___/

If yes, NDA # 20-239, 20-305 Drug Name Kytril (granisetron) Injection and Tablets, respectively

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

_____ _____

Signature of Preparer Date

Title:_____

/S/

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021238
Trade Name: KYTRIL (GRANISETRON HCL) 0.2MG/ML
Generic Name: GRANISETRON HCL
Supplement Number. 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: OP **Action Date:** 8/31/00
COMIS Indication: PREVENTION OF NAUSEA/VOMITING ASSOCIATED WITH INITIAL/REPEAT COURSES OF EMETOGENIC CANCER THERAPY. PREVENTION OF RADIATION INDUCED NAUSEA/VOMITING.

Indication #1: nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin
Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: New formulation developed with this submission
Comments (if any)

Lower Range	Upper Range	Status	Date
1 months	2 years	Deferred	6/30/04
Comments: No data available now.			
2 years	16 years	Completed	

Indication #2: nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.
Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
1 months	2 years	Waived	
Comments: No data available now.			
2 years	16 years	Waived	
Comments: Disease incidence too low (2%) for pediatric studies to be feasible. See 3/28/00 waiver letter.			

This page was last edited on 5/29/01

Signature

6/19/01
Date

DEBARMENT CERTIFICATION STATEMENT

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, SmithKline Beecham hereby certifies that, we did not use and will not use in any capacity, in connection with this New Drug Application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

Olivia Pinkett, Ph.D.

Olivia Pinkett

Director, Regulatory Affairs

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 21-238

Drug: Kytril (granisetron) Oral Solution

Sponsor: Hoffmann-La Roche Inc.

Material Reviewed

Submission Date(s): June 13, 2001, draft labeling

Receipt Date(s): June 14, 2001

Background and Summary Description: NDA 21-238, submitted August 30, 2000, provides for Kytril Oral Solution, a new dosage form that is bioequivalent to the currently approved Kytril Tablets. Kytril Tablets are indicated for the prevention of: 1) nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin; and 2) nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

On June 4, 2001 the Division asked the applicant to revise the draft package insert submitted with the NDA (via faxed, marked up draft labeling), based on a recommendation in the May 9, 2001 biopharmaceutics review. Specifically, the firm was asked to go throughout the package insert and replace references to "oral Kytril" with "Kytril Tablets" or "Kytril Oral Solution," as appropriate. The sponsor responded with a June 13, 2001 submission containing revised draft labeling that is the subject of this review.

Review

The submitted draft package insert (**coded HLR 06/13/01**) was compared to the marked up draft labeling faxed to the firm on June 4, 2001. As requested, the applicant has deleted references to "oral Kytril" and replaced them with "Kytril Tablets" or "Kytril Oral Solution," as appropriate.

According to the biopharmaceutics reviewer, Dr. Sandip Roy, these revisions are acceptable. (He did, however, note that the applicant is inconsistent with regard to the capitalization of the phrase "Kytril Tablets" and suggested that this be corrected.)

Conclusions

The submitted labeling is acceptable. The applicant will be requested to be consistent with regard to the capitalization of the phrase "Kytril Tablets."

6/27/01

/S/

Regulatory Health Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**OPDRA POSTMARKETING SAFETY REVIEW**	
TO: Lilia Talarico, M.D., Director Division of Gastrointestinal and Anticoagulant Drug Products HFD-180	**FROM:** Ann Corken Mackey, R.Ph., M.P.H., Safety Evaluator, Division of Drug Risk Evaluation I I (DDREII) HFD-440	**OPDRA PID #** D010026 January 23, 2001

DATE REQUESTED: January 9, 2001	**REQUESTOR/Phone #:**	
DATE RECEIVED:		
DRUG (Est): Ondansetron, granisetron, dolasetron	**NDA #** 20-781, 20-605, 20-103, 20-007, 20-403, 20-239, 20-305, [redacted], 20-623, 20-624	**SPONSOR:**
DRUG NAME (Trade): Zofran, Kytril, Anzemet	**THERAPEUTIC CLASSIFICATION:**	
EVENT: Ischemic colitis related to off-label use		

Executive Summary: An AERS search performed on January 16, 2001 (includes reports submitted between November 1997 and January 16, 2001) found no cases of ischemic colitis associated with the use of ondansetron, granisetron, or dolasetron. As of January 17, 2001 a MEDLINE search of the published English-language literature produced no reports of ischemic colitis associated with the use of these drugs. It should be recognized that these serotonin (5-HT3) receptor antagonists are currently approved for the prevention/treatment of emesis induced by cancer chemotherpay or preoperatively, and therefore are not used chronically like alosetron, but only as single dose or short-term treatment. Since there are no cases of ischemic colitis in AERS for ondansetron, granisetron, or dolasetron, we are unable to address off-label use for these drugs.

Reason for Request/Review:

Relevant Product Labeling

Search Date: January 16, 2001	**Search Type(s):** AERS Literature

Search Criteria: Drug Names: Ondansetron (Zofran), Granisetron (Kytril), Dolasetron (Anzemet)

MEDDRA Terms: *Ischemic colitis* (PT)

Search Results: As per the OPDRA consult of November 16, 2000 (NDA 21-107: Lotronex [alosetron] Safety & Risk Management Summary), no reports of ischemic colitis were found in AERS between November 1997 and October 2000 for serotonin (5-HT_3) receptor antagonists, including ondansetron, granisetron, or dolasetron. An AERS search performed on January 16, 2001 (includes reports submitted between November 1997 and January 16, 2001) found no cases of ischemic colitis associated with the use of ondansetron, granisetron, or dolasetron. As of January 17, 2001 a MEDLINE search of the published English-language literature produced no reports of ischemic colitis associated with the use of these drugs. Since there are no cases of ischemic colitis in AERS for ondansetron, granisetron, or dolasetron, we are unable to address off-label use for these drugs.

Discussion / Conclusions: An AERS search performed on January 16, 2001 (includes reports submitted between November 1997 and January 16, 2001) and reported in our previous consult found no cases of ischemic colitis associated with the use of ondansetron, granisetron, or dolasetron. As of January 17, 2001 a MEDLINE search of the published English-language literature produced no reports of ischemic colitis associated with the use of these drugs. It should be recognized that these serotonin (5-HT3) receptor antagonists are currently approved for the prevention/treatment of emesis induced by cancer chemotherpay or preoperatively, and therefore are not used chronically like alosetron, but only as single dose or short-term treatment. Since there are no cases of ischemic colitis in AERS for ondansetron, granisetron, or dolasetron, we are unable to address off-label use for these drugs.

Ann Mackey 01/23/01 **Reviewer's Signature / Date:**	**Lanh Green 01-23-01** **Team Leader's Signature / Date:**
Kathleen Uhl 01-23-01 **Acting Division Director Signature / Date:**	**Office Director Signature / Date:**
Attachments:	

Cc: **NDA # 20-781, 20-605, 20-103, 20-007, 20-403, 20-239, 20-305, 21-238, 20-623, 20-624**

HFD-103 Houn/Raczkowski

HFD-180 Division File/Div Dir/Kress/Gallo-Torres/Avigan/Project Manager

HFD-440 Uhl/Mackey/Piazza-Hepp/Green/Li/Dempsey//Drug

Electronic File Name:

MEMORANDUM OF TELECON

DATE: June 4, 2001

APPLICATION NUMBER: NDA 21-238, Kytril (granisetron) Oral Solution

BETWEEN:

Name: Anthony J. Corrado, Regulatory Affairs
Phone: (973) 562-3698
Representing: Hoffmann La-Roche Inc.

AND

Name: Melodi McNeil, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Request for Labeling Revisions

BACKGROUND: NDA 21-238 was submitted August 30, 2000 and provides for a new dosage form: Kytril Oral Solution. (Granisetron is currently approved in both tablet and injection formulations.) The primary user fee goal date is June 30, 2001.

The firm's proposed package insert was revised by the Division, based on the various review discipline recommendations, and faxed to the applicant. (The firm submitted revised immediate container and carton labeling on May 24, 2001, which, according to the chemistry reviewer, addressed each of the deficiencies described in the March 28, 2001 chemistry review. Accordingly, only a revised package insert was faxed to the firm.)

Note: The marked-up draft package insert was faxed to the firm is provided as an attachment.

TODAY'S PHONE CALL: I informed Mr. Corrado that marked-up draft labeling had just been faxed. I asked him to provide a response (in the form of revised draft labeling) as quickly as possible. The call was then concluded.

/S/ 6/13/01

Melodi McNeil
Regulatory Health Project Manager