CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-238

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-238

DISCIPLINE REVIEW LETTER

4/5/01

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

Dear Mr. Corrado:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron) Oral Solution.

We also refer to your submission dated October 18, 2000.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Regarding Drug Product Specifications:

   A. Your NDA described two types of specifications for drug product degradation Please clarify which limits will be used as part of the regulatory specifications.

   B. Tighten drug product specifications for the degradation products based on the stability data (

2. Characterize the structure and qualify any impurity that exceeds ICH guideline limits.

3. The description of the test methods No. CAM00056/1, CAM000602/2, CAM00061/1 and CAM 00059/2 could not be located (pages 066 and 067, volume 1.2). Please confirm that these methods numbers, listed on page 066-067 (volume 1.2), are the same methods described in volume 1.3 but under different numbers (e.g. PDMM 650/2, PDMM 689/1, PDMM650/2.2.1 PDMM 650, 2.3, etc.). Please provide consistent methods numbers throughout the NDA.

4. Provide details of the sampling plan used for the analytical tests and specifications for the drug product.

5. Please include the preservative efficacy test USP <51> in the stability testing for the above NDA batches. The test should be performed at time zero and at expiry date.

6. With respect to the stability of the drug product:

   A. Note that the stability data obtained from the qualification batches will be used as supportive data only, because they were manufactured for non US markets and used a

   B. Provide additional stability data from the validation NDA batches (more than the three months provided in the NDA). The validation NDA batches will be used for granting expiration dating for the drug product.

   C. Stability data should be provided to justify the labeling statement

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page} 4/5/01

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

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NDA 21-238

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

Dear Mr. Corrado:

We acknowledge receipt on December 26, 2000 of your December 22, 2000 correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug: Kytril® (granisetron) Oral Solution

NDA Number: 21-238

Name of New Applicant: Hoffmann-La Roche Inc.

Name of Previous Applicant: SmithKline Beecham Pharmaceuticals

Your correspondence provided the information necessary to effect this change and we have revised our records to indicate Hoffmann-La Roche Inc. as the sponsor of record for this application. Please note that all changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, require an approved supplement before implementation.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

/S/

{See appended electronic signature page}

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc: SmithKline Beecham Pharmaceuticals
Attention: Olivia Pinkett, Ph.D.
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Mail

NDA 21-238

INFORMATION REQUEST LETTER

SmithKline Beecham
Attention: Olivia Pinkett, Ph.D.
Director, NA Regulatory Affairs
1250 Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

OCT 11 2000

Dear Dr. Pinkett:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron) Oral Solution.

We are reviewing the Administrative section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide a signed debarment certification in accordance with the draft guidance for Industry entitled, "Submitting Debarment Certification Statements." This guidance is available electronically at http://www.fda.gov/cder/guidance/1700dft.pdf. Note that the use of conditional language such as "...to the best of our knowledge..." is not acceptable.

2. We note that Kytril Oral Solution is approved in several non-US countries. Please provide an English translation of the currently approved European Union labeling for this product.

3. According to the index, Item 3.0 ("SUMMARY"), G ("Clinical: Discussion of Safety") is in volume 1 of the submission, however, no specific page number was provided. Please either resubmit this information or provide its exact location in the application.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

/S/ Sincerely, /S/

10/11/00 10/10/00

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Incl

NDA 21-238

SmithKline Beecham
Attention: Olivia Pinkett, Ph.D.
Director, NA Regulatory Affairs
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

SEP 13 2000

Dear Dr. Pinkett:

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

Name of Drug Product: Kytril (granisetron hydrochloride) Oral Solution

Review Priority Classification: Standard (S)

Date of Application: August 30, 2000

Date of Receipt: August 31, 2000

Our Reference Number: NDA 21-238

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 30, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 30, 2001 and the secondary user fee goal date will be August 31, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic

Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

/S/ 9/13/00

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research