CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-238

Chemistry Review(s)

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21238/000**
Priority: **3S**
Org Code: **180**
Stamp: **31-AUG-2000** Regulatory Due: **30-JUN-2001**
Action Goal:
District Goal: **01-MAY-2001**
Applicant: **ROCHE**
340 KINGSLAND ST
NUTLEY, NJ 071101199
Brand Name: **KYTRIL (GRANISETRON HCL) 0.2MG/ML**
Established Name:
Generic Name: **GRANISETRON HCL**
Dosage Form: **LIQ (LIQUID)**
Strength: **0.2 MG/ML**

FDA Contacts:

M. MCNEIL	**(HFD-180)**	**301-827-7310**	**, Project Manager**
A. AL HAKIM	**(HFD-820)**	**301-827-7310**	**, Review Chemist**
L. ZHOU	**(HFD-180)**	**301-827-7471**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 01-JUN-2001 by M. GARCIA (HFD-322) 301-594-0095

Establishment:
DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment:
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-238 **REVIEW #:** 3 **DATE REVIEWED:** 06/01/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	11-MAY-01	14-MAY-01	14-MAY-01
AMENDMENT	14-MAY-01	15-MAY-01	18-MAY-01

NAME & ADDRESS OF APPLICANT: *Hoffmann-La Roche, Inc.*
340 Kingsland Street
Nutley
New Jersey 07110

DRUG PRODUCT NAME

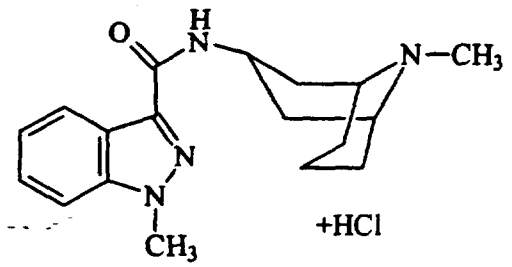
Proprietary: Kytril®
Established: Graniserton Hydrochloride
Code Name #: MP-123456B
Chem.Type/Ther.Class: 3/S

PHARMACOL. CATEGORY/INDICATION: Antinauseant and antiemetic agent.
Prevention of Nausea/Vomiting Associated with Initial/Repeat Courses of Emetogenic Cancer Therapy.
Prevention of Radiation Induced Nausea/Vomiting.

DOSAGE FORM: Solution
STRENGTHS: 2.24 mg/10 ml
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: √ Rx __ OTC
SPECIAL PRODUCTS: __ Yes √ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Endo-N-B-methyl-B-azabicyclo [3,3,1] non-3-yl-methyl-1H-indazole-3-carboxyamide



Molecular Weight: 348.9 (312.4 free base)
Molecular Formula: $C_{18}H_{24}N_4O$. HCl

SUPPORTING DMF DOCUMENTS:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
			Adequate	A. Al-Hakim	03/03/99
			Adequate	H. Sarker, HFD-150 02/25/2000	N/A
			Adequate	H. Sarker, HFD-150 08/16/2000	N/A

RELATED DOCUMENTS (if applicable):

IND) (granisetron hydrochloride injection)
IND) (granisetron hydrochloride Oral)
NDA 20,239 *Kytril*® (granisetron hydrochloride) Injection
NDA 20-305 *Kytril*® (granisetron hydrochloride) Tablets

Consults:	Date Submitted	Status
Division of Pharmaceutical Evaluation II	August 31, 2000	Approvable (05/08/01)
Microbiology	February 05, 2000	Approved (03/27/01)
Establishment Evaluation Report	September 28, 2000	Acceptable (06/01/01)

* This is a new dosage form for a previously approved drug product. Kytril is a registered trade name.

Remarks:
This review deals with amendments, dated May 11 and May 14, which contain responses to our information discipline review letter dated April 05, 01.

APPEARS THIS WAY ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The NDA may now be approved from the Chemistry, Manufacturing, and Controls point of view.
Based on the satisfactory real time stability data obtained from the NDA batches (12 months) and qualification batches (months), the applicant may be granted 12 months of expiry dating. However, the NDA applicant should be reminded that additional stability data (up to months) should be generated and submitted in the annual report.

/S/

Ali Al-Hakim, Review Chemist

/S/

Liang Zhou, Chemistry Team leader

cc:
Org. NDA 21-238
HFD-180/Division File
HFD-180/Ali Al-Hakim/05/24/01
HFD-180/Melodi McNeil
HFD-180/Liang Zhou
R/D Init by:
F/T 05/30/01

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01-JUN-2001 FDA CDER EES Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21238/000 Priority: 3S Org Code: 180
Stamp: 31-AUG-2000 Regulatory Due: 30-JUN-2001 Action Goal: District Goal: 01-MAY-2001
Applicant: ROCHE
340 KINGSLAND ST
NUTLEY, NJ 071101199
Brand Name: KYTRIL (GRANISETRON HCL) 0.2MG/ML
Established Name:
Generic Name: GRANISETRON HCL
Dosage Form: LIQ (LIQUID)
Strength: 0.2 MG/ML

FDA Contacts: M. MCNEIL (HFD-180) 301-827-7310 , Project Manager
A. AL HAKIM (HFD-820) 301-827-7310 , Review Chemist
L. ZHOU (HFD-150) 301-594-5765 , Team Leader

Overall Recommendation:

ACCEPTABLE on 01-JUN-2001 by M. GARCIA (HFD-322) 301-594-0095

Establishment:
DMF No:
AADA No:

Profile: LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-JUN-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment:
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-OCT-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: DRUG SUBSTANCE MANUFACTURER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-238 **REVIEW #:** 2 **DATE REVIEWED:** 05/30/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	11-MAY-01	14-MAY-01	14-MAY-01
AMENDMENT	14-MAY-01	15-MAY-01	18-MAY-01

NAME & ADDRESS OF APPLICANT: *Hoffmann-La Roche, Inc.*
340 Kingsland Street
Nutley
New Jersey 07110

DRUG PRODUCT NAME

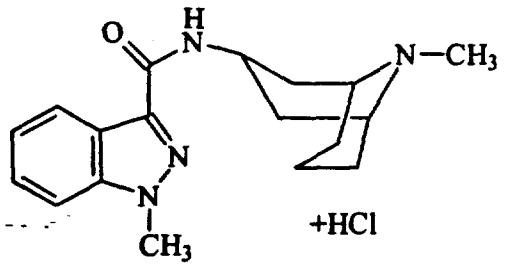
Proprietary: Kytril®
Established: Graniserton Hydrochloride
Code Name #: MP-123456B
Chem.Type/Ther.Class: 3/S

PHARMACOL. CATEGORY/INDICATION: Antinauseant and antiemetic agent.
Prevention of Nausea/Vomiting Associated with Initial/Repeat Courses of Emetogenic Cancer Therapy.
Prevention of Radiation Induced Nausea/Vomiting.

DOSAGE FORM: Solution
STRENGTHS: 2.24 mg/10 ml
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: √ Rx __ OTC
SPECIAL PRODUCTS: __ Yes √ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Endo-N-B-methyl-B-azabicyclo [3,3,1] non-3-yl-methyl-1H-indazole-3-carboxyamide



- Molecular Weight: 348.9 (312.4 free base)
  Molecular Formula: $C_{18}H_{24}N_4O$. HCl

SUPPORTING DMF DOCUMENTS:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
			Adequate	A. Al-Hakim	03/03/99
			Adequate	H. Sarker, HFD-150 02/25/2000	N/A
			Adequate	H. Sarker, HFD-150 08/16/2000	N/A

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Consults:	Date Submitted	Status
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Microbiology	February 05, 2000	Approved (03/27/01)
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* This is a new dosage form for a previously approved drug product. Kytril is a registered trade name.

Remarks:
This review deals with amendments, dated May 11 and May 14, which contain responses to our information discipline review letter dated April 05, 01.

APPEARS THIS WAY ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The NDA can be approve pending acceptable EER.

Based on the satisfactory real time stability data obtained from the NDA batches (12 months) and qualification batches (onths), the applicant may be granted 12 months of expiry dating. However, the NDA applicant should be reminded that additional stability data (up to nonths) should be generated and submitted in the annual report.

/S/

Ali Al-Hakim, Review Chemist

/S/

Liang Zhou, Chemistry Team leader

cc:
Org. NDA 21-238
HFD-180/Division File
HFD-180/Ali Al-Hakim/05/24/01
HFD-180/Melodi McNeil
HFD-180/Liang Zhou
R/D Init by:
F/T 05/30/01

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-238 **REVIEW #:** 1 **DATE REVIEWED:** 03/26/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-AUG-00	01-SEP-00	07-SEP-00
AMENDMENT	18-OCT-00	19-OCT-00	19-OCT-00

NAME & ADDRESS OF APPLICANT: *Hoffmann-La Roche, Inc.*
340 Kingsland Street
Nutley
New Jersey 07110

DRUG PRODUCT NAME

Proprietary: Kytril®
Established: Graniserton Hydrochloride
Code Name #: MP-123456B
Chem.Type/Ther.Class: 3/S

PHARMACOL. CATEGORY/INDICATION: Antinauseant and antiemetic agent.
Prevention of Nausea/Vomiting Associated with Initial/Repeat Courses of Emetogenic Cancer Therapy.
Prevention of Radiation Induced Nausea/Vomiting.

DOSAGE FORM: Solution
STRENGTHS: 2.24 mg/10 ml
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: √ Rx __ OTC
SPECIAL PRODUCTS: __ Yes √ No

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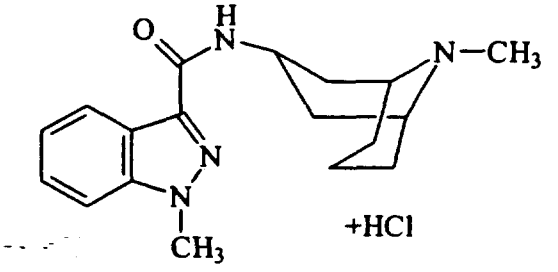

Molecular Weight: 348.9 (312.4 free base)
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SUPPORTING DMF DOCUMENTS:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
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NDA 20-305 *Kytril*® (granisetron hydrochloride) Tablets

Consults:	Date Submitted	Status
Division of Pharmaceutical Evaluation II	August 31, 2000	Pending
Microbiology	February 05, 2000	Pending
Establishment Evaluation Report	September 28, 2000	Pending

* This is a new dosage form for a previously approved drug product. Kytril is a registered trade name.

Remarks:
The firm reported, on page 00001, volume 1.1 that the oral solution is being proposed as an alternative to the tablet formulation of Kytril which is approved for the prevention of nausea and vomiting associated with emetogenic cancer therapy and with radiation. The equivalency of Kytril Oral solution and tablets is supported by study No. 308, which compared the bioequivalence of the approved 2 mg dose of the tablet formulation with a 2 mg dose of the oral solution formulation.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is Approvable from the Chemistry, Manufacturing and Controls point of view, however, the NDA applicant should provide additional information delineated in the draft deficiency letter at the end of this review.

/S/

Ali Al-Hakim, Review Chemist

cc:
Org. NDA 21-238
HFD-180/Division File
HFD-180/Ali Al-Hakim/12/28/00
HFD-180/Melodi McNeil
HFD-180/Liang Zhou
R/D Init by:
F/T 03/26/01

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DMF REVIEW

DMF Number: **DMF Type:** IV

TITLE:

1. CHEM REVIEW No. 1 **2. REVIEW DATE:** 02/08/01

3. ITEM REVIEWED

A. IDENTIFICATION:

B. LOCATION IN DMF: Volume 2.1

Type of Submission	Date of Submission	Location of Information
Amendment	03/03/1999	Volume 2.1

4. PREVIOUS DOCUMENTS: N/A

5. NAME & ADDRESS OF DMF HOLDER:

NAME:

ADDRESS:

6. DMF REFERENCED FOR:

NDA:	21-238	
APPLICANT NAME:	Hoffman-La Rouche, Inc.	
LOA DATE:	03/03/1999	
DRUG PRODUCT NAME:	Kytril	
DOSAGE FORM:	Solution	(CODE NAME: MP-123456B)
STRENGTH:	2.24mg/10ml	
ROUTE OF ADMINISTRATION:	Oral	

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: Not provided

DATES OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: No list was provided

9. CONSULTS: none

10. COMMENTS: have evaluated

Statement from the DMF holder indicated that all are approved for use in a regulation of the FDA.

11. CONCLUSION: Adequate

/S/ 02/08/01

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

DMF 1111 (2 copies)
HFD-180/Division File
HFD-180/A.Al-Hakim
HFD-180/L.ZHOU
HFD-181/M.McNeil
HFD-180/LTalarico
AA: 02/08/01