CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020305 (S001)

Trade Name: KYTRIL TABLETS

Generic Name: GRANISETRON HYDROCHLORIDE

Sponsor: SMITHKLINE BEECHAM PHARMACEUTICALS

Approval Date: 10/6/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020305 (S001)

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Medical Review(s)	X			
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EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)	X			
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020305 (S001)

APPROVAL LETTER

NDA 20-305/S-001

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

OCT - 6 1997

Dear Dr. Pinkett:

Please refer to your supplemental new drug application dated April 17, 1995, received April 17, 1995, resubmitted October 19, 1995 and received October 20, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron hydrochloride) Tablets.

We acknowledge receipt of your submission dated September 5, 1997, submitted in response to the August 21, 1997 approvable letter.

The supplemental application provides for a single 2 mg dose as an alternative to the 1 mg dose given twice daily.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated September 5, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on September 5, 1997.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-305/S-001. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Kati Johnson, Supervisory Consumer Safety Officer, at (301) 443-0487.

Sincerely yours,

10-3-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

10/3/97

cc:
Original NDA 20-305/S-001
HFD-180/Div. files
HFD-180/CSO/K.Johnson
HFD-002/ORM (with labeling)
HFD-103/Office Director
HFD-101/L.Carter
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)

APPEARS THIS WAY
ON ORIGINAL

Drafted by: kj/October 3, 1997/c:\wpfiles\cso\n\20305710.0kj
APPROVAL (AP)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020305 (S001)

APPROVABLE LETTER

NDA 20-305/S-001

AUG 21 1997

SmithKline Beecham Pharmaceuticals, Inc.
Attention: Olivia Pinkett, PhD
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-09890

Dear Dr. Pinkett:

Please refer to your supplemental new drug application dated April 17, 1995, received April 17, 1995, and resubmitted on October 19, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron) Tablets.

We acknowledge receipt of your submissions dated August 22, September 4, 1996, and February 20, 1997. The User Fee goal date for this application is August 21, 1997.

The supplemental application provides for a single 2 mg dose as an alternate to the currently approved 1 mg twice daily dose for the prevention of nausea and vomiting associated with cancer chemotherapy, including high dose cisplatin.

We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft labeling. In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-

up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Kati Johnson, Supervisory Consumer Safety Officer, at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

LT 8-20-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

APPEARS THIS WAY
ON ORIGINAL

KJ 8/19/97

cc:
Original NDA 20-305/S-001
HFD-180/Div. Files
HFD-002/ORM
HFD-103/Office Director
HFD-101/L.Carter
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-180/CSO/K.Johnson
Drafted by: kj/August 13, 1997/c:\wpfiles\cso\n\20305708.0kj
APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020305 (S001)

MEDICAL REVIEW(S)

JUN - 3 1997

MEDICAL OFFICER'S REVIEW

NDA 20-305/S-001

KYTRIL® (granisetron hydrochloride) tablets

Supplemental New Drug Application

Prevention of Nausea and Vomiting Associated With Initial and Repeat Courses of Emetogenic Cancer Therapy Including High-dose Cisplatin

2 mg daily (single dose) to be given 1 hour before chemotherapy

Submitted by SmithKline Beecham

Reviewer:
Hugo E. Gallo-Torres, M.D., Ph.D.
HFD-180

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	20-305/S-001
Date Submitted:	February 20, 1997
Sponsor:	SmithKline Beecham Pharmac. King of Prussia, PA
Drug:	KYTRIL® (granisetron hydrochloride) tablets
Route of Administration:	Oral
Proposed Indication:	2 mg once-a-day dose for Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Cancer Chemotherapy, Including High-dose Cisplatin. (The 2 mg once-a-day dose is an alternative to the approved 1 mg b.i.d. regimen)

I. BACKGROUND/INTRODUCTION

KYTRIL® (granisetron•HCl = GRAN) is a selective binder to the 5-HT_3 receptor available in tablet (and injection) dosage forms for the following indication: prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy, **including high dose cisplatin.** The approved tablet formulation is 1 mg b.i.d. In this regimen, the first 1 mg tablet is given up to 1h. before chemotherapy and the second tablet, 12h after the first.

The present amendment to supplement S-001, the object of the present review, is submitted in support of the claim that a 2 mg dose (two 1 mg GRAN tablets), taken as a single daily dose prior to chemotherapy, is an adequate dose regimen alternate to the currently approved dose regimen of 1 mg two times daily.

Supplement S-001 was initially submitted April 17, 1995 and resubmitted October 19, 1995. In support of their request the sponsor submitted results of two clinical trials:

- **Study 215**, an active-active comparison (GRAN 2 mg µ.i.d. vs 1 mg b.i.d.), 2-arm, randomized, multicenter study carried out under double-blind conditions. The study was stratified by gender.

  This study design was considered somewhat useful, with two main constraints. In the absence of an internal comparator, either PL or a low dose of the antiemetic, it is not possible to demonstrate that any of the two dose regimens is effective (comparison to historical control would be needed). The emetogenic stimulus used in this trial was primarily cyclophosphamide-based and of moderate emetogenic potential. In addition, this study did not include "high-dose cisplatin".

- **Study 436**, a 1 arm, uncontrolled, multicenter, open-label trial was considered to be less useful.

This is because open-label observations are not conducive to the minimization of bias required to appropriately demonstrate efficacy. Using this approach the sponsor attempted to show efficacy by comparing the results of study 436 to those of study 022 (GRAN 1 mg b.i.d., in original NDA 20-235) and study 012 (PL response after **intravenous** 5-min. infusion).

The adequacy of studies 215 and 436 was reviewed by the MO (MOR of October 10, 1996). On the basis of his assessment of the evidence, the MO did not recommend approval of that supplemental application. The deficiencies were communicated to the sponsor in a letter dated October 16, 1996 (see Recommendations for Regulatory Action, MOR of October 10, 1996). In essence, the deficiencies were summarized as follows:

- In Study 215, the 2 mg daily dose appears to be equivalent to the 1 mg twice daily dose for complete response and for no nausea, but no data has been provided to demonstrate that either arm was active.

  In an attempt to show effectiveness, the MO compared the results for both 2 mg daily and 1 mg twice daily doses to two relevant historical controls: granisetron 0.25 mg twice daily (from Study 021), and prochlorperazine 10 mg twice daily (from Study 288). Using this approach, we could not demonstrate that the dose regimens (2 mg daily or 1 mg twice-a-day) were effective in this study. In addition, the results for complete response were lower than expected, and might represent total response rates rather than complete response rates. [This was eventually shown to be the case.]

  [The conclusion was reached that the demonstration of bioequivalence in study 215 was not convincing.]

- In the second trial (Study 436), the effectiveness difference confidence intervals, for comparing the new granisetron dose regimen with historical positive control of the granisetron twice daily dose regimen, **were quite wide and inconclusive** for supporting the hypothesis of clinical equivalence between the new and approved granisetron dose regimen. [Study 436 supported neither effectiveness nor equivalence.]

The present amendment (February 20, 1997) to supplement S-001 contains the sponsor's responses to the issues specified in FDA letter of October 6, 1996. The sponsor's approach consists of the following:

1. A comparison of the results for Study 215 for the Kytril® treatment groups to the prochlorperazine (PCPZ) group (historical control from study 288).

   The purpose of this comparison is to validate that the active treatments of study 215 are effective in the trial. Results of study 288 were previously reviewed by the MO. This was a two-arm (Kytril® 1 mg b.i.d. vs oral PCPZ 10 mg b.i.d.), double-blind, randomized, parallel group, multicenter study in patients receiving moderately emetogenic, non-

cisplatin regimens. This study (288) is cited in the prescribing information for the tablets. The primary efficacy parameter stipulated in protocol 288 was **total control**.

[1]

2. Submission of results of Study 402.

   The objective of this approach is to further substantiate the efficacy of Kytril® 2 mg, given once a day. Study 402 was a second trial in which moderately emetogenic regimens were given. The primary objective of study 402 was to compare the efficacy of 2 mg once daily, given orally, with that of 32 mg i.v. OND. Patients received concomitant prophylaxis with dexamethasone. The experimental arm consisted of those GRAN 2 mg once-a-day treated patients that did not receive prophylaxtic dexamethasone. These were compared as a group to the PCPZ historical control in Study 288.

3. Addressing the efficacy of a single 2 mg dose of Kytril® in high dose cisplatin patients

   For this purpose, the sponsor submitted results of Study 341 which (as Study 402), was set to compare efficacy of 2 mg once in comparison to 32mg i.v. ondansetron. Concomitant prophylactic dexamethasone was permitted in this study. The experimental arm consisted of those patients who did not receive prophylactic dexamethasone. Results from this arm were compared as a group to the GRAN 1 mg b.i.d. group from Study 022 (historical positive control group).

It is to be worth noting that both comparative regimens are cited in studies contained in the prescription information for Kytril®.

NOTE: During the review of the evidence it is important to realize that results of studies 215 and 288 have previously been assessed, in detail, by the MO. Therefore, only key data, primarily dealing with results, are reviewed here. A similar approach (simplification of presentation of data) is being used when evaluating results of studies 402 and 341.

II. COMPARISON OF THE GRAN TREATMENT GROUPS OF STUDY 215 TO THE PCPZ GROUP OF STUDY 288

- Included in this comparison were 356 patients who received GRAN 1 mg b.i.d. and 344 who received 2 mg once daily (both from Study 215) and 111 PCPZ patients from Study 288. As shown in Table 1, the three treatment groups exhibited no marked or statistically significant differences with respect to baseline demographic characteristics, distribution by most common cancer site and most common chemotherapeutic agents administered. All differences were within 15% and given the sample size of 111 of the historical control, these differences are not expected to be statistically significant.

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[1] Total control, a more stringent assessment of efficacy than Complete Response, is defined as no vomiting, no rescue medication and no nausea (not even mild nausea).

TABLE 1
Studies 215 and 288

Data Showing Comparability of Groups on Demographics, Type of Cancer and Chemotherapeutic Agents

Study 215 (GRAN)			
Demographic Characteristic	1 mg b.i.d. n=356	2 mg once daily n=344	Study 288 PCPZ 10 mg b.i.d. n=111
A. Demographics			
Gender:			
Male	29%	29%	16%
Female	71%	72%	84%
Mean Age (y)	55.3	56.0	59.3
Race:			
Black	12%	12%	12%
Caucasian	82%	85%	81%
Other	6%	3%	7%
Weekly Alcohol Consumption (Units)	3.6	4.7	2.4
B. Most Common Site of Disease and Malignancies			
Breast Cancer	49.7%	50.1%	62.2%
Lymphoma	15.7%	13.7%	7.2%
Lung	12.1%	14.3%	15.3%
C. Most Common Chemotherapeutic Agents (>10%) Administered			
Cyclophosphamide	73%	75%	81%
Doxorubicin	49%	52%	39%
Fluorouracil	39%	39%	54%
Carboplatin	17%	15%	32%
Methotrexate	16%	17%	32%
Etoposide	13%	13%	32%
Vincristine	11%	15%	11%
Cisplatin	11%	13%	---

- Given the size of the effect and the above-mentioned comparability results of the patient characteristics, the historical control used as a comparator **is adequate.** According to the FDA statistician (M. Huque, review of April 18, 1997) the size of the effect in comparison to the historical control is convincing in that the lower 95% confidence intervals are **consistently well above zero.**

- The efficacy results are summarized in Table 2.

- The results of Study 215 (Table 2) suggest that the 2 mg once-a-day GRAN regimen is clinically not worse than the already approved 1 mg b.i.d. dose for the stated indication. Using Complete Response as the parameter of evaluation the therapeutic gain (2 mg once-a-day vs historical control) was clinically meaningful (28%).

TABLE 2
Studies 215 and 298

Efficacy Results at 24h

Efficacy Endpoints	Study 215 (GRAN) 1 mg b.i.d. n=356	Study 215 (GRAN) 2 mg once daily n=344	PCPZ 10 mg b.i.d. [Study 288] n=111	Therapeutic Gain 2 mg once vs Historical Control	95% CI 1 mg b.i.d. vs Historical Control	95% CI 2 mg once vs Historical Control
Complete Response	69.8%	64.0%	41.4%	**28.4%**	17.0% to 37.8%	12.0% to 33.0%
No Vomiting	81.9%	76.5%	48.2%	**28.3%**	23.6% to 43.9%	18.1% to 38.9%
No Nausea	51.4%	52.5%	35.1%	**16.3%**	5.95% to 26.6%	6.98% to 27.7%
Total Control	50.6%	50.4%	33.3%	**17.1%**	Therapeutic Gain 2 mg once vs Historical Control	6.8% to 27.4%

III. SUPPORTIVE EVIDENCE FROM STUDY 402

- Study 402, completed in April 1996, was entitled "*A Double-Blind, Multicenter, Parallel Study Comparing the Efficacy and Safety of Oral Granisetron Hydrochloride 2 mg With IV Ondansetron Hydrochloride 32 mg, Given Once, in the Prevention of Nausea and Vomiting Induced by IV Cyclophosphamide-Based or Carboplatin-Based Chemotherapy in Patients With Malignant Disease*"

- The study used a double-blind, multicenter, parallel group design. A total of 1085 patients were randomized (GRAN, n=542; OND, n=543). A

total of 106 investigators from the U.S., Puerto Rico and Canada participated in the trial. Patients were stratified to treatment by their use or non-use of costicosteroids.

- Included in the trial was a sub-group of 101 GRAN (2 mg once-a-day) treated patients who did not receive corticosteroids. Results in this sub-group were compared to a historical control. The latter consisted of the PCPZ 10 mg b.i.d. group in Study 288 (see above).

- As shown in Table 3, the two groups were comparable in their demographic characteristics. The sponsor did not present clear evidence regarding comparability of group re: types of cancer and chemotherapy received.

TABLE 3
Studies 402 and 288

Data Showing Comparability of Groups in Demographics

Demographic Characteristic	GRAN 2 mg once daily [sub-group from Study 402] n=101	PCPZ 10 mg b.i.d. [Group From Study 288] n=111
Gender:		
Male	30%	16%
Female	70%	84%
Mean Age (y)	55.3	59.3
Race:		
Black	14%	12%
Caucasian	75%	81%
Other	11%	7%

- The efficacy results are summarized in Table 4. Using Complete Response as the parameter of evaluation, the therapeutic gain (2 mg once-a-day vs PCPZ 10 mg b.i.d.) was clinically meaningful (17%). It can be seen that none of the confidence intervals depicted in Table 4 include zero. This is indicative of supporting evidence in favor of the effectiveness of the GRAN 2 mg once-a-day dose regimen.

TABLE 4
Studies 402 and 288

Efficacy Results at 24h

Efficacy Endpoints	GRAN 2 mg once daily [sub-group from Study 402] n=101	PCPZ 10 mg b.i.d. [Group from Study 288] n=111	Therapeutic Gain 2 mg once vs Historical Control	95% CI for the absolute difference
Complete Response	58.4%	41.4%	17.0%	3.61%, 30.33%
No Vomiting	79.2%	48.2%	31.0%	18.71%, 43.34%
No Nausea	50.5%	35.1%	15.4%	2.09%, 28.63%
Total Control	49.5%	33.3%	16.2%	1.99%, 28.37%

IV. SUPPORTIVE EVIDENCE FROM STUDY 341

- Study 341, completed in 1996, was entitled, *"A Double-Blind, Multicenter, Parallel Study Comparing the Efficacy and Safety of Oral Granisetron Hydrochloride 2 mg With IV Ondansetron Hydrochloride 32 mg, Given Once, in the Prevention of Nausea and Vomiting Induced by Cisplatin-Based Chemotherapy"*

- This study made use of a double-blind, multicenter (a total of 103 U.S. investigational sites), parallel group design. A total of 1054 patients (GRAN, n=534, OND, n=520) were randomized into either group of the trial. The use of prophylactic dexamethasone or methyl prednisone was allowed in the study.

- Included in the trial was a sub-group of 117 GRAN (2 mg once-a-day) - treated patients who did not receive prophylactic corticosteroid. Results in this sub-group were compared to those of two historical controls. The latter consisted of 1) GRAN 1 mg b.i.d. dose group in Study 022 and 2) placebo group of Study 012.

- As shown in Table 5, the three groups were comparable in their demographic characteristics. They were also comparable in the mean cisplatin dose roughly 80 mg/m^2. This cisplatin dose is considered highly emetogenic.

TABLE 5
Studies 341, 022 and 012

Data Showing Comparability of Groups on
Demographics and Mean Cisplatin Dose (mg/m^2) Infused

Demographic Characteristic	GRAN 2 mg once daily [sub-group from Study 341] n=117	GRAN 1 mg b.i.d. [Group from Study 022] n=119	Placebo [Group from Study 012] n=14
Gender:			
Female	33%	60%	43%
Male	67%	40%	57%
Mean Age (y)	60.5	54.9	61.1
Race:			
White	79%	77%	100%
Black	14%	19%	0
Other	7%	3%	0
Mean Body Weight (lbs)	161.5	141.1	142.2
Mean Cisplatin Dose (mg/m^2)	80.9	80.0	80.5

- Efficacy Results are depicted in Table 6. GRAN 2 mg once-a-day was effective in comparison to the placebo historical control of study 012. Using Complete Response as the parameter of evaluation. The Therapeutic gain was clinically meaningful (37%).

Table 6
Studies 341, 022 and 012

Efficacy Results at 24 h

Efficacy Endpoint	GRAN 2 mg once daily [sub-group from Study 341] n=117	GRAN 1 mg b.i.d. [group from Study 022] n=111	Placebo [Group from Study 012] n=14	Therapeutic Gain GRAN 2 mg once daily vs placebo Historical Control	95% CI 2 mg once vs 1 mg bid (Study 022)	95% CI 2 mg once vs placebo (Study 012)
Complete Response	52 (44.4%)	41.4%	1 (7.1%)	37.3%	**-5.1,20.4%**	**20.9, 53.7%**
No vomiting	68 (58.1%)	48.2%	2 (14.3%)	43.8%	**-1.8,23.7%**	**23.2, 64.4%**
No nausea	54 (46.2%)	35.1%	1 (7.1%)	39.1%	**-9.2,-16.2%**	**22.6, 55.4%**
Total control	47 (40.2%)	33.3%	1 (7.1%)	33.1%	**-9.1,16.2%**	**16.7, 49.3%**

In addition, the lower 95% confidence interval for the difference GRAN 2 mg once-a-day minus GRAN 1 mg b.i.d. with respect to response rates are well within 10%. According to these results, the effectiveness of the 2 mg dose of GRAN is not inferior to that of GRAN 1 mg b.i.d.

V. REVIEWER'S OVERALL CONCLUSIONS

1. The sponsor's retrospective analysis suggests that the active control in Study 215 is effective when compared to the historical control PCPZ of Study 288. On the basis of these results, the trial is valid for clinical equivalence efficacy testing.

2. The efficacy data of Study 215 suggest that the 2 mg once a day dose regimen is clinically not inferior to the already approved 1 mg bid dose in the prevention of nausea and vomiting in cancer patients receiving chemotherapy regimens moderate emetogenic potential.

3. The findings summarized under 1. and 2. above are supported by retrospective historical control analyses in sub-group of patients treated with GRAN 2 mg once-a-day in studies 402 and 341.

VI. RECOMMENDATION FOR REGULATORY ACTION

Approval of the GRAN 2 mg once-a-day dose regimen as an alternative to the approved 1 mg b.i.d. regimen is recommended.

Both GRAN regimens are effective in the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.

June 3, 1997

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-305/S-001
HFD-180
HFD-180/LTalarico LT 6-3-97
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
r/d 5/28/97 jgw/deg
f/t deg: 5/29/97/6/3/97
GEN\20305705.0HG

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

OCT 10 1996

MEDICAL OFFICER'S REVIEW

NDA 20-305/S-001

KYTRIL® (granisetron hydrochloride) tablets

Supplemental New Drug Application

Prevention of Nausea and Vomiting Associated With Initial and Repeat Courses of Emetogenic Cancer Therapy Including High-dose Cisplatin

2 mg daily (single dose) to be given 1 hour before chemotherapy

Submitted by SmithKline Beecham

Reviewer:
Hugo E. Gallo-Torres, M.D., Ph.D.
HFD-180

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	20-235/S-001
Date Submitted:	October 19, 1995 (Study CPMS-215) June 14, 1996 (Study P-436)
Sponsor:	SmithKline Beecham Pharmac. King of Prussia, PA
Drug:	KYTRIL® (granisetron hydrochloride) tablets
Route of Administration:	Oral
Proposed Indication:	2 mg once-a-day dose for Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Cancer Chemotherapy, Including High-dose Cisplatin. [The 2 mg once-a-day dose is an alternative to the approved 1 mg b.i.d. regimen]
First Draft to Supervisor:	September 6, 1996
Review Completed:	October 10, 1996

Material Reviewed:

Submitted On October 19, 1995:	Volume
(Item 1): Index, Summary [Position Paper Included], Draft Labeling	1
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Submitted On June 14, 1996:	Volume
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MOR, NDA 20-235/S-001

TABLE OF CONTENTS (Selected Sections)

I. Introduction

KYTRIL® (granisetron•HCl=GRAN), a selective binder to the 5-HT_3 receptor, is available in two dosage forms, injection and tablets, for the same indication: prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. KYTRIL® injection is approved at the single dose of 10 μg/Kg, given 30 min. before the initiation of chemotherapy [and only of the day(s) the chemotherapy is given]. Final action for NDA 20-239/S-004 (30-second infusion; reviewed by MO, who recommended approval, concurrence by Division Director on June 13, 1996) is pending. The approved tablet formulation is 1 mg b.i.d. In this regimen, the first 1 mg tablet is given up to 1 hour before chemotherapy and the second tablet, 12 hours after the first.

Supplement S-001, the object of the present review, is submitted in support of the claim that a 2 mg dose (two 1 mg GRAN tablets) taken as a single daily dose prior to chemotherapy is an adequate dose regimen alternate to the currently approved dose regimen of 1 mg two times daily. The aim of the present review is to assess the adequacy of the two clinical studies in Supplement 001.

II. Studies Submitted in Support of the Efficacy of GRAN 2 mg Once-a-Day (two 1 mg tablets) Dose Regimen

Listed in Table 1 are the identification, number of patients, main features of design, emetogenic potential of the chemotherapeutic regimen and the groups being compared in the two clinical trials submitted in NDA 20-235/S-001. Initial comments on the usefulness (mainly efficacy) of these studies (identified as A. and B.) is given on the last column of Table 1.

TABLE 1
NDA 20-235/S-001

Identification, Number of Patients, Main Features of Design, Study Population, Emetogenic Potential and Doses Being Compared in the Two Clinical Trials Submitted in Support of the Approval of GRAN 2 mg once-a-day Regimen as an Alternate to the Approved 1 mg b.i.d. Dose Regimen

Study Identification No. of Patients	Main Design Features	Study Population	Emetogenic Potential	Groups Being Compared	Remarks
A. MY-1031/BRL-043694A/2/CPMS-215 [n=700] F=499 M=201 (USA)	2-arm, double-blind, stratified by gender, randomized, multicenter. Efficacy and safety assessed over the 24h period following chemotherapy adm. Open-label evaluations during 15 consecutive cycles of chemotherapy. Primary Efficacy Parameter was **Complete Response**, as in previous trials.	Adult (≥18y) M or F cancer patients, chemotherapy naive, with Karnofsky performance status score of at least 60%, with "acceptable" vital signs, hematology and clinical chemistry results. The site of primary malignant neoplasm was breast (50%), lymphoma (15%), lung (13%) and ovary (6.5%).	<u>Moderate</u> Although 12% of the patients received cisplatin of low to moderate emetogenic potential and 16% of the patients received carboplatin, most patients received cyclophosmide (74%), doxorubicin (51%) or 5-FU (39%)-based regimens.	GRAN 2 mg uid, 1h prior to chemo-therapy [n=344] F=246 M=98 vs GRAN 1 mg b.i.d. 1h prior to chemotherapy and 12h after the first dose [n=356] F=253 M=103	• Somewhat useful design (active vs active comparison). • Efficacy is demonstrated by showing clinical equivalence of the 2 mg once-a-day dose to the approved 1 mg b.i.d. regimen, in the same trial. • But in the absence of an internal comparator, either PL or a low dose of the compound, it is not possible to demonstrate that any of the two dose regimens is effective (comparison to historical control is needed). • Because the ratio of F/M in each arm is 2.5, stratification of patients on the basis of gender is important, not only to achieve balanced groups but also to assess efficacy in females in comparison to males (or the other way around). • An additional constraint when analyzing data from this trial is that the emetogenic stimulus is mostly cyclophosphamide-based and of **moderate emetogenic potential**. This study did not include "high-dose cisplatin".

TABLE 1 (Con't)

B. 43694A/436 [n=30] F=8 M=22 USA	1-arm, uncontrolled, open-label, multi-center. Efficacy and safety assessed over the 24-h period following chemo-therapy administration. Primary Efficacy Parameter was Total Control of symptoms. Secondary Efficacy parameters included No Vomiting, No Nausea and Complete Response.	Adult (≥18y) M or F cancer patients, chemotherapy-naive, without "unstable medical disorders", with Karnofsky performance status ≥60, no signs or symptoms of intracranial pressure from primary or secondary brain tumors, not scheduled to receive radiation therapy. The site of the primary malignant neoplasm was respiratory/ intrathoracic (53%), digestive organs (20%), genito/urinary (17%) and other sites (10%)	Moderately High The mean cisplatin dose was 77.6 mg/m², with a range of But the length of administration of cisplatin is not given.	GRAN 2 mg u.i.d. 1h prior to chemotherapy. (one arm) No internal comparator.	• Less useful design. • Open-label observations do not conduce to the minimization of bias required to appropriately demonstrate efficacy. • The sponsor attempts to show efficacy by comparing the results of this trial to those of study 022 (GRAN 1 mg b.i.d., in original NDA 20-235) and Study 012 (PL response after intravenous 5-min. infusion). • The adequacy of the above-proposed comparisons to demonstrate efficacy will be assessed. • It is important to keep in mind that the parameter **Total Response** is very stringent. • Meanwhile, the MO wishes to point out that the F/M ratio in Study -436 is 0.4 (very different from the 2.5 observed in the above trial). Thus, an important issue to be addressed during the review of the evidence is **gender response**.

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III. Study CPMS-215

"A double blind comparison of the efficacy of two dose regimens of oral granisetron (1 mg twice, 2 mg once) in preventing acute nausea and vomiting in patients receiving **moderately emetogenic chemotherapy**. SB Report MY-1031/BRL-043694/1/CPMS-215."

1. Objective

This trial was set to compare the efficacy and safety of oral GRAN•HCl regimens, 2 mg u.i.d and 1.0 mg b.i.d (the approved dosing regimen), in preventing N&V induced by moderately emetogenic chemotherapeutic agents.

2. Study Design

This was a double-blind, parallel group, multicenter study. Eligible patients were stratified by gender and randomized into one of the 2-arms of the trial. Efficacy and safety were assessed over the 24-h period following chemotherapy administration during the initial and subsequent cycles of chemotherapy. The performance of oral GRAN was monitored over 16 consecutive cycles of chemotherapy.

3. Study Population

As listed below, the criteria for inclusion were adequate for this type of study.

INCLUSION CRITERIA

(1) Chemotherapy-naive, adult (≥18y) M and F cancer patients

(2) scheduled to receive one of the following chemotherapeutic agents, either as a single agent or in combination:

• I.V. cyclophosphamide	≥500 mg/m²
• oral cyclophosphamide	≥100 mg/m²
• dacarbazine	≥300 mg/m²
• doxorubicin	>40 mg/m² (single agent) ≥25 mg/m² (in combination)
• carboplatin	≥300 mg/m²
• cisplatin	≥20 mg/m² to ≤50 mg/m²

(3) Karnofsky performance status score of at least 60% or an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less

(4) "acceptable" vital signs, hematology and clinical chemistry results [The meaning of "acceptable" was not explained]

(5) receiving no concurrent medications with significant antiemetic activity

(6) no nausea and/or vomiting within the 24-h period prior to the administration of test medication

(7) signed IC; willingness and ability to comply with the protocol directives.

4. Highlights of Study Execution/Efficacy and Safety Assessment

- Patients were screened within one week of their scheduled chemotherapy, and were stratified by gender and randomized into one of the two arms of the trial. Patients remained at the clinical trial site for at least one hour after chemotherapy. At discharge, patients were given test medication for the 12-h administration. They also were provided a diary and instructed to record the number of episodes of vomiting, episodes of nausea and severity of nausea at 6-h intervals for the 24-h period following chemotherapy. AEs, use of rescue antiemetic and non-antiemetic concomitant medications also were recorded. Following completion of cycle 1 of chemotherapy, patients were given the opportunity to receive open-label GRAN 2 mg u.i.d, on the first day of each subsequent cycle of chemotherapy.

- For the First Cycle of chemotherapy, the **primary efficacy parameters** that were assessed at the end of the 24-h post-chemotherapy period were:

  (a) the proportion of patients with no vomiting

  (b) the proportion of patients with no nausea and

  © the proportion of patients who experienced **complete response** (defined as no vomiting, no more than mild nausea, no antiemetic rescue).

  The **secondary efficacy parameters** that were assessed were:

  (a) the frequency of emesis during the 24-h period

  (b) the frequency and maximum severity of nausea

  and

  © the incidence and frequency of antiemetic rescue medication.

- For subsequent cycles of chemotherapy, that is for patients participating in the open-label phase of the trial, only complete response was assessed during each subsequent cycle.

5. Test Medications/Maintenance of Blinding

- To maintain the double-blind character of the trial, each patient received two tablets (either one GRAN tablet and one PL or two GRAN tablets, depending upon the randomized regimen) one hour prior to chemotherapy. A second dose of test medication (either one GRAN tablet and one PL or two PL tablets, depending upon the randomized regimen), was taken by the patient 12h after the first dose.

- Blinded test medication was packaged with 4 tablets per package, labeled Dose 1 and Dose 2, to be given as mentioned above.

- The GRAN and PL tablets were identical in appearance.

6. Statistical Methodology

- The efficacy of oral GRAN 2 mg u.i.d versus oral GRAN 1 mg b.i.d. was examined against a two-tailed alternative with a nominal type I error rate $\alpha=0.05$. The study was designed to provide 80% power to detect a 10% difference in response between treatments **with an assumed average response of 75%.**

- The comparability of treatment groups was assessed. For categorical variables (e.g., Gender and Race), comparability was assessed by means of the Chi-square test of independence provided by SAS (proc FREQ). Baseline comparability for continuous variables (e.g., Age and Alcohol Consumption) was tested by a one-way ANOVA (proc GLM). Because of the variety of chemotherapeutic agents employed, emetogenic stimulus was compared by visual inspection of the distribution of individual agents.

- Statistical comparisons of treatment were based on the proportions of patients achieving each primary endpoint. Because stratified randomization was employed, the Cochran-Mantel-Haenszel procedure (proc FREQ) was used to control for stratum membership (i.e., gender). Thus, results for each primary endpoint were presented for males, females and the combined strata.

- Each primary endpoint was displayed as the number of patients achieving a successful outcome out of the total randomized and the corresponding percentage with 95% confidence intervals. In addition, 95% confidence intervals for the difference in proportions were constructed. These were based on the following calculation:

$$\text{Difference} = (\text{GRAN 1 mg} \times 2) - (\text{GRAN 2 mg} \times 1)$$

- Finally, p-values obtained from the Cochran-Mantel-Haenszel Chi-square statistic (proc FREQ), which control for gender, were provided.

- Secondary endpoints were summarized and displayed via descriptive statistics. The frequency of emesis and frequency of antiemetic rescue were summarized as continuous outcomes. Within each treatment group, the mean, minimum, maximum and SD were calculated. Maximum Severity of Nausea (i.e., None, Mild, Moderate or Severe) and Incidence of Antiemetic Rescue Use (i.e., YES or NO) were treated as categorical variables. The number and percent of patients achieving each distinct outcome were reported for each randomized treatment group.

7. Results

a. Participating Investigators/Patient Accounting

- The study was conducted by 74 investigators at 64 sites within the USA.
- A total of 700 cancer patients received test medication in the first cycle of chemotherapy (ITT Population), and were included in the safety assessments.
- 3 patients did not receive chemotherapy.
- Thus the ITT Population for assessment of efficacy was 697 patients.
- 406 of the 700 patients who were enrolled in Cycle 1 of the trial continued to receive open-label GRAN 2 mg u.i.d. in subsequent cycles of chemotherapy.

b. Withdrawals/Completed Patients

As shown below, the number of patients withdrawn due to AEs or lack of efficacy and protocol violations were similar between the two treatment groups. Ten less patients in the 2 mg u.i.d. group completed the 24-h study (n=331) than in the 1 mg b.i.d. group (n=341). This numerical difference is not expected to influence the efficacy results.

	GRAN 2 mg u.i.d. (n=344)	GRAN 1 mg b.i.d. (n=356)
Reason for Withdrawal		
AE	1	2
Lack of Efficacy	4	2
Protocol	7	10
Violation		
Other Reasons	1	1
Completed Cycle	331	341

c. Comparability of Groups/Patient Baseline Characteristics

As shown in Table 2, the two groups were comparable to each other in demographic characteristics, primary disease site, Karnofsky status, ECOG scale and chemotherapy agents. In this trial, 71.5% of the patients were female, while 28.5 were male, the mean age was 55.5 years (range 18 to 88 years). Half of the patients had breast cancer, 15% had lymphoma, 13% had cancer of the lung; 6.5% had cancer of the ovaries. Cancer of the testis, soft tissue sarcoma, head/neck and cervix occurred in 3% or less of the patients; location for other cancers was 36% for the rest of the patients. The most commonly used primary chemotherapeutic agent was cyclophosphamide (74% of the patients), followed by doxorubicin (50.5%), 5-FU (38%) and MTX (16.5% of the patients). As per platinum-based regimens, carboplatin was given to 16% of the patients and cisplatin to 12% of the patients. The emetogenic potential of the chemotherapeutic agents are best characterized as being mainly non-cisplatin and of **moderate emetogenic potential**.

d. Cycles 2 through 10: Recorded Reasons for Patient Withdrawal/Number of Patients Evaluated for Efficacy (Table 3)

This Table lists the number of patients participating in chemotherapy cycle 2 through 10 (the number of patients per Cycle 11 through 16 was 7 or less per cycle). In Table 3, a steady decrease in the number of patients completing Cycle 2 through 10 is documented (Cycle 2, n=406, Cycle 10, n=11).

TABLE 2
Study -215

Demographic and Baseline Disease Characteristics

	GRAN 2 mg, u.i.d. [n=344]	GRAN 1 mg, b.i.d. [n=356]
A. DEMOGRAPHICS		
Male	98 (28%)	103 (29%)
Female	246 (72%)	253 (71%)
Mean Age (y)	56	55
Range (y)		
Race		
Caucasian	291 (85%)	293 (82%)
Black	41 (12%)	43 (12%)
Other	9 (3%)	16 (5%)
Oriental	3 (<1%)	4 (1%)
B. PRIMARY DISEASE SITE		
Breast	50%	50%
Lymphoma	14%	16%
Lung	14%	12%
Ovary	6%	7%
Testis	2%	3%
Soft Tissue Sarcoma	<1%	2%
Head/Neck	2%	1%
Cervix	<1%	<1%
Other	11%	10%
Karnofsky Status (>90%)	112/146 (77%)	123/158 (78%)
ECOG Scale (≤1%)	189/197 (96%)	185/198 (93%)
C. CHEMOTHERAPEUTIC AGENTS[a,b]		
Cyclophosphamide	75%	73%
Doxorubicin	52%	49%
Fluorouracil	39%	39%
Carboplatin	15%	17%
Methotrexate	17%	16%
Etoposide	13%	13%
Vincristine	15%	11%
Cisplatin	13%	11%
D. MOST FREQUENTLY USED RESCUE MEDICATION		
Prochlorperazine	13.1%	11.2%

a) There were some differences in the proportion of patients receiving chemotherapeutic agents as a function of gender.
Females: Cyclophosphamide (88%), doxorubicin (55%), 5-FU (51%)
Males : Cyclophosphamide (39%), doxorubicin (39%), etoposide (34%), cisplatin (31%) or vincristine (29%)

TABLE 3
Study -215

Number of Patients Completing Cycles 2 through 10.
Recorded Reasons for Patient Withdrawal

	GRAN 2 mg u.i.d., Cycle No./[Number of Pts. Completing Cycle]								
	2 [406]	3 [332]	4 [256]	5 [151]	6 [110]	7 [43]	8 [34]	9 [18]	10 [13]
Withdrawn									
Adverse Event	6	3	2	1	2	0	0	0	1
Lack of Efficacy	23	21	5	9	1	1	0	1	0
Protocol	8	3	3	2	0	0	3	0	0
Violation									
"Other Reasons"	14	20	18	12	4	3	3	1	1
Completed Cycle	**355**	**285**	**228**	**127**	**103**	**39**	**28**	**16**	**11**

e. Clinical Response (Table 4)

i) Response in the first 24-h (Cycle 1) (Table 4)

- Whether assessing results in the Protocol-Defined or the ITT Population there were no statistically significant differences between the 2 mg u.i.d. group vs the 1 mg b.i.d. for all three endpoints, namely complete response, no emesis or no nausea.

ii) Response in female vs male patients

- As also shown in Table 4, for each of the three endpoints and in both study populations (Protocol-Defined and ITT) and in both arms of the study the response in female patients was numerically lower than in males. This is illustrated below for the parameter Complete Response.

	Complete Response in		Δ (F-M)
	FEMALE	MALE	
GRAN 2 mg u.i.d.			
Protocol-Defined	46%	60%	-14%
ITT	47%	61%	-14%
GRAN 1 mg b.i.d.			
Protocol-Defined	44%	59%	-15%
ITT	46%	63%	-17%

TABLE 4
Study -215

Summary of Clinical Response
First 24-h (Cycle 1)

Stratum	Endpoint	GRAN		Difference % (95% CI)	p-value[b]
		2 mg u.i.d.	1 mg b.i.d.		
A. PROTOCOL DEFINED POPULATION					
Combined	CR[a]	151/306 (49%)	152/314 (48%)	-0.9 (-8.8, 6.9)	N.S.
	No emesis	235/306 (77%)	258/314 (82%)	5.4 (-1.0, 11.7)	N.S.
	No nausea	157/306 (51%)	155/314 (49%)	-1.9 (-9.8, 5.9)	N.S.
Female	CR	103/223 (46%)	101/228 (44%)	-1.9 (-11.1, 7.3)	N.S.
	No emesis	166/223 (74%)	182/228 (80%)	5.4 (-2.4, 13.1)	N.S.
	No nausea	107/223 (48%)	104/228 (46%)	-2.4 (-11.6, 6.8)	N.S.
Male	CR	48/83 (58%)	51/86 (59%)	1.5 (-13.4, 16.3)	N.S.
	No emesis	69/83 (83%)	76/86 (88%)	5.2 (-5.3, 15.8)	N.S.
	No nausea	50/83 (60%)	51/86 (59%)	-0.9 (-15.7, 13.8)	N.S.
B. INTENT-TO-TREAT POPULATION					
Combined	CR	173/343 (50%)	179/354 (51%)	0.1 (-7.3, 7.6)	N.S.
	No emesis	263/343 (77%)	290/354 (82%)	5.2 (-0.8, 11.3)	N.S.
	No nausea	180/343 (53%)	182/354 (51%)	-1.1 (-8.5, 6.4)	N.S.
Female	CR	116/245 (47%)	115/252 (46%)	-1.7 (-10.5, 7.1)	N.S.
	No emesis	182/245 (74%)	200/252 (79%)	5.1 (-2.3, 12.5)	N.S.
	No nausea	120/245 (49%)	118/252 (47%)	-2.2 (-10.9, 6.6)	N.S.
Male	CR	57/98 (58%)	64/102 (63%)	4.6 (-9.0, 18.1)	N.S.
	No emesis	81/98 (83%)	90/102 (88%)	5.6 (-4.2, 15.3)	N.S.
	No nausea	60/98 (61%)	64/102 (63%)	1.5 (-11.9, 15.0)	N.S.

a) CR = Complete Response
b) p-value by M-H test

iii) Additional parameters for the first 24-h (Cycle 1)

As summarized below, there were no statistically significant differences between the two treatment groups in regard to no nausea, the severity of nausea, the use of no antiemetic rescue and the frequency of vomiting or antiemetic rescue.

	GRAN		Δ
	2 mg u.i.d.	1 mg b.i.d.	
No Nausea	180 (53%)	182 (51%)	2%
MILD	77 (22%)	99 (28%)	-4%
MOD	46 (13%)	38 (11%)	2%
SEV	39 (11%)	34 (10%)	1%
No Antiemetic Rescue	270 (79%) [74.5, 83.1]	284 (80%) [76.2, 84.5]	-1%
Frequency of Vomiting Mean (S.D.M.) Range	[n=342] 0.78 (2.31)	[n=352] 0.69 (2.27)	0.09
Frequency of Antiemetic Rescue Mean (S.D.M.) Range	[n=343] 0.55 (1.29)	[n=354] 0.52 (1.31)	0.03

iv) Complete Response rates over 24-h for repeat chemotherapy cycles (Table 5)

Depicted in this Table are the response rates for the open-label extension of the trial, where the patients received GRAN 2 mg once-a-day (only). The complete response rates, particularly for Cycles 6 through 10, were numerically greater in magnitude than for Cycle 1. The higher therapeutic gain seen in M in comparison to F recorded in Cycle 1 was also observed in some but not all of the Cycles after Cycle 1 [this is denoted in Table 5 as Δ (F-M) for each Cycle]. Except perhaps for Cycles 2 through 4, the previously observed higher response rates in M than F patients was inconsistent.

f. Results of Safety Evaluations

i) Incidence of AEs in Cycle 1 (Table 6)

As shown in this Table, the overall incidence of all AEs was very similar between the groups (2 mg u.i.d.=87%; 1 mg b.i.d.=88%). The most commonly reported AEs in the GRAN 2 mg u.i.d. group were: headache (26%), fatigue (17%), constipation (14%) and granulocytopenia (11%). These incidences were similar to those reported in the GRAN 1 mg b.i.d. group [headache=24%, fatigue (18%), constipation (12%) and granulocytopenia (11%)].

TABLE 5
Study -215

Complete Response Rates Over 24-Hours for Repeat Chemotherapy Cycles

Cycle	2 [n=405] n (%)	3 [n=331] n (%)	4 [n=254] n (%)	5 [n-149] n (%)	6 [n=109] n (%)	7 [n=43] n (%)	8 [n=34] n (%)	9 [n=17] n (5)	10 [n=13] n (%)
All	238 (58.8%)	195 (58.9%)	145 (57.1%)	89 (59.7%)	68 (62.4%)	34 (79.1%)	23 (67.6%)	12 (70.6%)	10 (76.9%)
Female	159 (53.5%)	137 (56.6%)	105 (54.7%)	68 (60.2%)	53 (62.4%)	22 (75.9%)	17 (68.0%)	8 (66.7%)	7 (77.8%)
Male	79 (73.1%)	58 (65.2%)	40 (64.5%)	21 (58.3%)	15 (62.5%)	12 (85.7%)	6 (66.7%)	4 (80.0%)	3 (75.0%)
(F-M)	-19.6	-8.6	-9.8	1.9	0.1	-7.9	1.3	-13.3	2.8

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TABLE 6
Study -215

AEs Occurring in ≥5% of the Patient Population

Cycle 1

	GRAN	
	2 mg u.i.d. [n=344] n (%)	1 mg b.i.d. [n=356] n (%)
All Patients	**299 (87%)**	**312 (88%)**
Nausea[a]	134 (39.0%)	136 (38.2%)
Headache	88 (25.6%)	84 (23.6%)
Vomiting[b]	76 (22.1%)	82 (23.0%)
Fatigue	57 (16.6%)	64 (18.0%)
Constipation	49 (14.2%)	44 (12.4%)
Granulocytopenia	39 (11.3%)	38 (10.7%)
Fever	31 (9.0%)	37 (10.4%)
Diarrhea	27 (7.8%)	38 (10.7%)
Anorexia	14 (4.1%)	29 (8.1%)
Dyspepsia	19 (5.5%)	23 (6.5%)
Insomnia	17 (4.9%)	25 (7.0%)
Abdominal Pain	19 (5.5%)	19 (5.3%)
Rigors	17 (4.9%)	21 (5.9%)
Dizziness	17 (4.9%)	18 (5.1%)
Leukopenia	18 (5.2%)	17 (4.8%)
Serious AEs[c]	**27 (10.8%)**	**40 (11.2%)**

a,b) Episodes of N&V during the 24-h assessment period were considered an indication of lack of efficacy.
c) The most frequently reported serious AEs were under the system white cell reticuloendothelial (granulocytopenia) and body as a whole (fever). Serious AEs were generally regarded as not being related to test medication.

ii) Severity of AEs in Cycle 1

[These data are not shown].

- No differences between the two dosing regimens were seen in the distribution of AEs by severity.
- Most of the events reported were mild or moderate in severity.

- Headache was the most frequently reported severe AE, occurring at comparable frequencies in the two treatment groups.
- The majority of events reported were considered by the investigator to be unrelated to test medication.
- Headache, constipation, diarrhea, vomiting and nausea were the events most often considered to be related or possibly related to test medication.
- No differences in the distribution of investigator-determined relationships were seen between the two dosing groups.

iii) AEs during repeat cycles of chemotherapy (Cycle 2 through 6) (Table 7)

This Table displays the proportion of patients that experienced one or more AEs during Cycles 2 through 6 of chemotherapy, with open-label 2 mg u.i.d. GRAN. Aside from N&V, headache was the most commonly reported event during repeat cycles of chemotherapy and GRAN treatment. Fatigue, granulocytopenia, alopecia and anemia were also frequently reported.

TABLE 7
Study -215

Adverse Events that Occurred in ≥5% of Patients During Repeat Cycles of Chemotherapy Cycle 2 through Cycle 6

	GRAN 2 mg u.i.d., Cycle No.				
	2 [n=406] n (%)	3 [n=332] n (%)	4 [n=256] n (%)	5 [n=151] n (%)	6 [n=110] n (5)
Patients With AEs	**316 (78%)**	**269 (81%)**	**190 (74%)**	**108 (72%)**	**76 (69%)**
AE (Preferred Term)					
Nausea	121 (30)	104 (31)	60 (23)	38 (25)	14 (13)
Fatigue	52 (13)	55 (17)	26 (10)	16 (11)	5 (5)
Headache	81 (20)	62 (19)	32 (13)	20 (13)	15 (14)
Vomiting	56 (14)	51 (15)	37 (15)	18 (12)	12 (11)
Granulocytopenia	42 (10)	35 (11)	34 (13)	11 (7)	9 (8)
Alopecia	40 (10)	19 (6)	5 (2)	4 (3)	4 (4)
Anemia	19 (5)	26 (8)	14 (6)	11 (7)	4 (4)
Fever	30 (7)	22 (7)	15 (6)	1 (1)	3 (3)
Constipation	32 (8)	24 (7)	12 (5)	6 (4)	3 (3)
Diarrhea	26 (6)	13 (4)	12 (5)	9 (6)	2 (2)
Dyspepsia	20 (5)	12 (4)	8 (3)	6 (4)	1 (1)
URI	15 (4)	12 (4)	7 (3)	3 (2)	5 (5)

URI = Upper Respiratory Infection

- A total of 57 (14%) of the 406 who entered into repeat cycles of chemotherapy reported serious AEs. As with the first cycle of chemotherapy, the most frequently reported serious events were classified under the systems white cell and reticuloendothelial (granulocytopenia) and body as a whole (fever). Serious AEs were generally regarded as not being related to GRAN.

  - Patient (PID 215.061.1445) received 4 mg GRAN (2 mg b.i.d.) in Cycle 2 and 3 mg GRAN (2 mg and 1 mg 12 hours later) in Cycle 3. The patient experienced no ill effects. The overdose was judged to be related to GRAN.

iv) AE withdrawals and deaths

As presented in sponsor's Table VI (vol. 2, p. 000100), a total of 18 patients W/D from the trial (all chemotherapy cycles combined) due to AEs. In 4 patients, the underlying AEs (abnormal ALT, AST values in two patients and headache with the other two), were considered to be related to GRAN. This information is summarized below.

Withdrawals Assessed as Possibly Related to GRAN

Pt. Identification	GRAN Dose at time of Withdrawal	Cycle	Reason for W/D
215.010.0218	2 mg u.i.d.	2	Abnormal AST, ALT
215.012.0265	2 mg u.i.d.	6	Severe headache
215.026.0601	2 mg u.i.d.	5	↑ AST, ↑ ALT
215.055.1302	2 mg u.i.d.	2	Headache

- 19 deaths were reported [sponsor's Table VII]. None of the deaths were considered to be related to GRAN. Disease progression was the most common cause of death.

v) Laboratory/Vital signs data

There were little changes between screen and follow-up values and between the two dosing regimens for post-Tx results of the hematology and clinical chemistry parameters. Similarly, no differences were noted between dosing groups in the proportion of patients that experienced changes in vital signs [sponsor's Table VIII].

8. Conclusions (Sponsor)

This clinical study comparing oral granisetron 1 mg b.i.d. and oral granisetron 2 mg u.i.d. showed that:

- "The dosing regimens, granisetron 1 mg b.i.d. and 2 mg u.i.d., are comparably effective in preventing the acute (<24 hrs) nausea and vomiting associated with emetogenic chemotherapy in chemotherapy naive patients;

- "Granisetron 2 mg u.i.d. is effective in preventing the acute (<24 hrs) nausea and vomiting in repeat cycles of emetogenic chemotherapy;

- "Granisetron dosing regimens, 1 mg b.i.d. and 2 mg u.i.d., are safe and well tolerated by cancer patients."

9. Reviewer's Comments

Study -215 is one of the two clinical trials submitted by the sponsor of NDA 20-235/S-001 in support of the claim that a 2 mg dose (given as two 1 mg GRAN tablets), taken as a single daily dose prior to chemotherapy, is an adequate dose regimen alternate to the currently approved dose regimen of 1 mg twice-a-day.

Study -215 was an active-active comparison of the proposed dose regimen (2 mg u.i.d.) to the approved regimen (1 mg b.i.d.). This randomized trial was set to show **equivalence** and was conducted under double-blind, stratified by gender, multicenter conditions. In this trial, the emetogenic stimulus was of moderate emetogenic potential and primarily non-platinum-based, although 12% of the patients were given cisplatin (at low to moderate emetogenic rates) and 16% received carboplatin (also at moderate emetogenic rates). A total of 74% of the patients received cyclophosphamide-, 51% doxorubicin-, and 39% 5-FU-based regimens, all of which were of **moderate emetogenic potential**. It is worth reiterating that study -215 did not include patients receiving "high dose cisplatin".

A very detailed review of the demographic and disease characteristics pre-drug allows the conclusion that the randomization process was well executed. The two experimental groups were comparable to each other in demographic parameters as well as primary disease site, (primary malignancy site), Karnofsky status, distribution of cancer chemotherapeutic agents and most frequently used rescue medication. All of these similarities are in support of the comparisons for bioequivalence.

On the basis of the above balances between the two experimental groups, the reviewer agrees with the sponsor's conclusion that the dosing regimens, GRAN 2 mg u.i.d. and 1 mg b.i.d. are comparably effective in preventing the acute (<24h) N&V associated with moderate emetogenic potential. However, although clinical equivalence has been demonstrated, as pointed out in Table 1 of this review, in the absence of a negative comparator, it is not possible to demonstrate that any of the two dose regimens is efficacious. The trial design was deficient in that it did not include an arm that could be used as a comparator. Such a needed comparator could be PL, a low dose of GRAN, or another "active" comparator tested at a low dose. This approach would show that both the 2 mg uid arm and the 1 mg b.i.d. arm are independently superior

to the comparator. In the absence of such an internal comparator, the reviewer has chosen two historical comparators. Both comparators are derived from the clinical trials (Studies 021 and 288) included in the labeling for Kytril® tablets, demonstrating that the 1 mg b.i.d. GRAN regimen is efficacious.

Prior to assessing efficacy using these historical data, it is important to document that the reviewer's proposed historical comparators are **relevant**. In summary Table 7a, a comparison is given of the mean features of design, demographics and disease characteristics in the three groups of patients being compared. In short, the three groups were comparable in most respects. In all three groups, there was a predominance of female patients, with a ratio F/M ranging from 2.5 to 6.4. Most patients were white and of approximately the same age . Breast, lung, lymphoma and ovary were the primary cancer sites.

For most patients, the primary chemotherapeutic agent was cyclophosphamide. This was followed by other non-cisplatin-based regimens and these were all of moderate emetogenic potential. Of note, the proportion of patients receiving cisplatin in Studies -215, -021 and -288 was 13%, 8% and 0%, respectively. The proportion of those receiving carboplatin was 15%, 9% and 20% of the patients in each of the three trials, respectively. Of those receiving cisplatin, most were given <50 mg/m^2. This is a rate considered associated with moderate emetogenic potential. In summary then, as we have repeatedly noted, the chemotherapeutic regimens used in these trials can be characterized as being of moderate emetogenic potential and did not include "high dose cisplatin".

Since, as shown in Table 7a, the three groups were reasonably balanced in most of the factors that matter and all the patients received moderately emetogenic primary non-cisplatin-based regimens, the results may be compared to assess the effectiveness of the 2 mg once-a-day GRAN arm from Study -215. Results of these analyses are summarized in Table 7b. Listed in this Table are the proportion of patients with complete response, those who experienced no emesis and those who experienced no nausea (not even mild nausea) in the two arms of study -215, the two pertinent arms from the four in Study 021 and the two arms in Study 288. In Table 7b, for studies 021 and 288, the reviewer has added the results with the 1 mg Kytril® b.i.d. in order to document the observation that, all in all, the Complete Response values in Study 215 (51%) were much lower than the values in studies 021 (81%) and 288 (74%). For every efficacy parameter being evaluated, presented are the response in the combined population and the results as a function of gender. The objective of the reviewer's approach is to assess the efficacy of each of the two arms in study 215 against the negative controls in the other two trials. Except for CR in Study 021, Table 7b demonstrates a consistently higher response in males than in females (denoted as M>F), with therapeutic gains ranging from 6% to up to 30%, depending on the trial and parameter of evaluation being compared.

TABLE 7a
Study -215

Design, Demographics, Primary Cancer Types and Emetogenic Stimulus in Study 215 and the Reviewer's Proposed Negative Comparator Groups Derived from Studies 021 and 288

			NEGATIVE COMPARATORS	
Arm Being Compared →		Study 215 Oral Two 1 mg Kytril® tablets, once	Study 021 Oral GRAN 0.25 mg b.i.d.	Study 288 Oral PCPZ[a] 10 mg b.i.d.
NUMBER OF PATIENTS		344	229	111
Design		One of 2-arms, double-blind, stratified by gender, randomized, parallel-group, multi-center	One of 4-arms[b], double-blind, randomized, parallel group, multi-center	One of 2-arms[c], double-blind, randomized, parallel group, multi-center
Gender	Females Males	246 (72%) 98 (28%)	198 (86%) 31 (14%)	93 (84%) 18 (16%)
F/M Ratio		2.5	6.4	5.2
Mean Age	(y) Range	56	52	59
Race	White Black Other	291 (85%) 41 (12%) 12 (4%)	Not Available	90 (81%) 13 (12%) 21 (19%)
Primary Cancer Types		Breast 172 (50%) Lung 49 (14%) Lymphoma 47 (14%) Ovary 22 (6%) Other 38 (11%)	Breast 162 (71%) Ovary 23 (10%) Lung 15 (7%) Lymphoma 10 (4%) Other 19 (8%)	Breast 69 (62%) Lung 17 (15%) Lymphoma 8 (7%) Ovary 6 (6%) Other 8 (7%)
Primary Chemotherapeutic Agents		CYCLOPH. 258 (75%) DOXORUBICIN 179 (52%) 5-FU 134 (39%) CARBOPLATIN 52 (15%) MTX 58 (17%) VINCRISTINE 52 (15%) ETOPOSIDE 46 (13%) CISPLATIN 44 (13%)	CYCLOPH. i.v. 129 (56%) CYCLOPH. p.o. 27 (12%) CARBOPLATIN 20 (9%) CISPLATIN 19 (8%) DACARBZINE 1 (<1%) OTHERS 33 (14%)	CYCLOPHOSPHAM. 90 (81%) 5-FU 60 (54%) DOXORUBICIN 43 (39%) MTX 36 (32%) CARBOPLATIN 22 (20%) VINCRISTINE 12 (11%)

a) PCPZ = prochlorperazine
b) The other three arms were: GRAN, at the oral dose of 0.5, 1.0 and 2.0 mg b.i.d.
c) The other arm consisted of Kytril®, 1 mg b.i.d.

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TABLE 7b
Study -215

Clinical Response in Each of the Two Arms of Study 215 in Comparison to Response in Each of the Two Relevant Historical Controls

	Study 215		Study 021		Study 288	
	Two 1 mg Kytril® tablets once	1 mg Kytril® b.i.d.	GRAN 1 mg b.i.d.	GRAN 0.25 mg b.i.d.	GRAN 1 mg b.i.d.	PCPZ 10 mg b.i.d.
GROUP	A	B	C	D	E	F
COMPLETE RESPONSE						
Combined	173/343 (50%)	179/354 (51%)	189/233 (81%)	140/229 (61%)	87/118 (74%)	46/111 (41%)
F	116/245 (47%)	115/252 (46%)	166/205 (81%)	117/198 (59%)	63/92 (69%)	35/93 (38%)
M	57/98 (58%)	64/102 (63%)	23/28 (82%)	23/31 (74%)	24/26 (92%)	11/18 (61%)
M>F	+11%	+17%	+1%	+15%	+23%	+23%
NO EMESIS						
Combined	263/343 (77%)	290/354 (82%)	204/233 (88%)	150/229 (66%)	97/118 (82%)	53/110 (48%)
F	182/245 (74%)	200/252 (79%)	178/205 (87%)	128/198 (65%)	72/92 (78%)	42/92 (46%)
M	81/98 (83%)	90/102 (88%)	26/28 (93%)	22/31 (71%)	25/26 (96%)	11/18 (61%)
M>F	+9%	+9%	+6%	+6%	+18%	+15%
NO NAUSEA						
Combined	180/343 (53%)	182/354 (51%)	146/233 (63%)	109/229 (48%)	68/118 (58%)	39/111 (35%)
F	120/245 (49%)	118/252 (47%)	123/205 (60%)	91/198 (46%)	47/92 (51%)	29/93 (31%)
M	60/98 (61%)	64/102 (63%)	23/28 (82%)	18/31 (58%)	21/26 (81%)	10/18 (56%)
M>F	+12%	+16%	+22%	+12%	+30%	+25%

The therapeutic gains [2 mg u.i.d. GRAN in Study 215 vs each of the two negative controls and 1 mg b.i.d. in Study 215 vs each of the two negative controls in the other two studies] and the respective p-values for these

comparisons are depicted in Table 7c. [Note that therapeutic gains and statistical calculations for 1 mg b.i.d. GRAN in Studies 021 and 288 are not presented because this dose regimen has already been shown to be superior to each of the internal comparators in each of these two pivotal trials. These are the data displayed in the Kytril® labeling and it would be unnecessarily repetitious to show these differences here].

The results of these statistical evaluations exemplify the difficulties encountered when using historical controls to demonstrate efficacy.

TABLE 7c
Study -215

Therapeutic Gain (%Δ) and p-values: Clinical Response Arising From Comparisons of Each of the Two Arms in Study 215 (A and B) to the Response in Each of the Two Relevant Historical Controls (D and F) (see Table 7b)

	% Δ Between Groups/[2-Sided p-values]			
	A [GRAN 2 mg once a day] VS		B [GRAN 1 mg b.i.d.] VS	
	D	F	D	F
COMPLETE RESPONSE				
Combined	-11% [p=0.013]	+ 9% [p=N.S.]	-10% [p=0.012]	+10% [p=N.S.]
F	-12% [p=0.0167]	+ 9% [p=N.S.]	-13% [p=0.0058]	+ 8% [p=N.S.]
M	-16% [p=N.S.]	- 3% [p=N.S.]	-11% [p=N.S.]	+ 2% [p=N.S.]
NO EMESIS				
Combined	+11% [=0.003]	+31% [p=0.001]	+16% [p=0.001]	+34% [p=0.001]
F	+ 9% [p=0.0291]	+28% [p=0.001]	+14% [p=0.0006]	+33% [p=0.001]
M	+12% [p=N.S.]	+22% [p=0.038]	+17% [p=0.0450]	+27% [p=0.004]
NO NAUSEA*				
Combined	+ 5% [p=N.S.]	+18% [p=0.001]	+ 3% [p=N.S.]	+16% [p=0.003]
F	+ 3% [p=N.S.]	+18% [p=0.003]	+ 1% [p=N.S.]	+16% [p=0.011]
M	+ 3% [p=N.S.]	+ 5% [p=N.S.]	+ 5% [p=N.S.]	+ 7% [p=N.S.]

NOTE: For males some of the differences of greater than 1% are not significant because of small sample size.

Through the evaluations depicted in Tables 7b and 7c the reviewer attempts to answer the following two key questions, primarily on the basis of Complete Response, probably the most important (primary) parameter of efficacy.

Question 1: Is Kytril 2 mg once-a-day active?

Answer: If one considers complete response, the primary efficacy parameter of evaluation used in so many studies with 5-HT_3 receptor antagonists, the answer to this question is **NO**. The comparisons in Table 7c do not show A to be **superior** to either D or F. On the contrary, for two parameters (CR in females and CR combined), the 2 mg dose was shown to be statistically **inferior** to D (0.25 mg b.i.d.) [p=0.013 and 0.0167, respectively]. It seems that a reasonable conclusion from these comparisons is that the 2 mg once-a-day regimen from Study -215 is not different from either of the two negative comparators [the 0.25 mg b.i.d. derived from Study 021 or the PCPZ 10 mg b.i.d. derived from Study 288].

Results of secondary efficacy parameters of evaluation are summarized below.

If one uses NO EMESIS as the parameters of evaluation, effectiveness [statistically significant difference between the 2 mg once-a-day arm in Study -215 and the historical controls] seems to be shown for all subgroups, except Males (in the comparison A vs D for males).

If one uses NO NAUSEA as the parameter of evaluation, none of the comparisons between A vs D yield statistically significant differences. In the comparisons A vs F, statistical significance was shown for female and combined but not male subgroups.

A reasonable conclusion when using NO EMESIS and NO NAUSEA as parameters of evaluation is that some inconsistent activity (of the 2 mg once-a-day regimen) is shown.

Question 2: Is Kytril 1 mg b.i.d. active?

[This question is asked in the context of the present approach of using a) historical comparators and b) a "new" 1 mg b.i.d. arm (from Study 215)].

Answer: As depicted in Table 7c, the therapeutic gains (or losses) between B vs D or F are all very similar to those described in detail above for the comparisons A vs D or F. Also, with one exception [NO EMESIS in male patients, which was significant for the 1 mg b.i.d. (B) but not for the 2 mg once-a-day (A) when compared to D (0.25 mg b.i.d.)], all statistical comparisons between 1 mg b.i.d. originating from Study 215 to the two historical comparators were very similar to those comparing 2 mg once-a-day to the historical comparators.

Therefore, using CR as the parameter of evaluation, the 1 mg b.i.d. was not different from either 0.25 mg b.i.d. or the PCPZ 10 mg b.i.d. Similarly, when using NO EMESIS and NO NAUSEA as parameters of evaluation, a reasonable

conclusion is that these historical control evaluations show some inconsistent efficacy (of the 1 mg b.i.d.).

Overall, the conclusions from Study 215 are as follows.

- The newly proposed regimen of oral Kytril 2 mg once-a-day is of comparable effectiveness to the approved 1 mg b.i.d. regimen. Both GRAN regimens prevent the acute (<24h) N&V associated with moderate emetogenic potential from primarily non-cisplatin regimens.

- But Study 215 has not shown whether any of these two regimens is active. On the contrary, using Complete Response, the most important parameter of evaluation, at this particular trial, both the newly proposed and the approved regimen are both shown to be equally inactive when compared to what the reviewer considers to be **relevant comparators**. Of course we do not know if the two arms of Study -215 may be shown to be active when compared to other historical controls, namely **placebo or no treatment**.

- However, the 1 mg b.i.d. approved regimen has previously shown to be effective in at least two well-controlled trials and this was the basis for approval of this oral regimen of GRAN. At this point, it is important to recognize that compounds (drugs) do not show activity all the time, in all studies.

- But the main issue is to demonstrate that the 2 mg once-a-day regimen is active. But this demonstration fails when using the relevant historical comparators chosen by the reviewer.

IV. STUDY P-436

"An Open-label, Uncontrolled, Multicenter Study to Evaluate the Efficacy and Safety of Two 1 mg Tablets of Kytril® (granisetron hydrochloride) Given Once Prior to Chemotherapy in the Prevention of Nausea and Vomiting Induced by Cisplatin-based Chemotherapy"

1. Objectives

   a. To evaluate the efficacy of a single 2 mg dose of Kytril® Tablets given once prior to chemotherapy in preventing acute nausea and vomiting in patients receiving cisplatin-based chemotherapy.

   b. To assess the safety and tolerance of a single 2 mg dose of Kytril® Tablets given once prior to chemotherapy.

TABLE 8
Study -436

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• At least 18y old M or F adult patients, with malignancies. • Naive to emetogenic chemotherapy. • Scheduled to receive cisplatin-based chemotherapy, at a dose of at least 60 mg/m² (alone or in combination with other agent or agents). Minimum cisplatin dose had to be based on the patient's actual B_{wt}. • Males had to be surgically sterilized, or agreed to practice adequate contraception during the study. • Females of non-childbearing potential (i.e., those who had been surgically sterilized, or who were at least one-year post-menopausal) may have entered the study. Females of child-bearing potential had to have a negative pregnancy test (urine or serum hCG) before entry into the study, had to agree to practice adequate contraceptive precautions during the study. • Signed IC. APPEARS THIS WAY ON ORIGINAL	• Participation in any drug trial in which the patient received an investigational drug within 30 days or 5 half-lives (whichever was longer) preceding the screening phase of this study. • Any unstable medical disorder. [This was not defined.] • Karnofsky performance status score <60. • Chronic (>1 month) or concurrent (Day 0 and through 24h) treatment with agents known to have significant antiemetic activity[a]. - Narcotic analgesics were not permitted except if the patient had received these within the past week and had no nausea or emesis. Prohibited medications were allowed after the 24-h period of assessment. - The use of short-acting agents administered for procedures (such as port insertion) was permitted up until 8h before test medication administration[b]. • Primary or secondary (from metastatic disease) brain tumors with signs or symptoms of increased intracranial pressure. • Known hypersensitivity to any $5HT_3$-receptor antagonist. • Unwillingness or inability to comply with the study protocol. • Radiation therapy to any abdominal field (T10-L5) within 24h before the dose of study medication was given, or during the 24-h period of assessment (Study Days 0-1). Radiation to other fields was acceptable (e.g. pelvic irradiation, thoracic irradiation). • Any nausea within 1 hour and/or emesis (vomiting and/or retching) within 24h before dosing with test medication. These patients were rescheduled and enrolled if they were able to meet the criterion on another day.

a) Examples of these were:
- antihistamines (e.g. promethazine, diphenhydramine); non-sedating antihistamines were acceptable
- antipsychotics - (e.g. phenothiazines, butyrophenones)
- cannabinoids
- corticosteroids (except for replacement or maintenance doses up to 10 mg prednisone or equivalent).
- metoclopramide

b) Benzodiazepines were also withheld for the 8h period before test medication on Day 0 and were not allowed during the 24-h assessment period. DEX was allowed for patients treated with taxol, but had to be given prior to 24h before administration of cisplatin (time 0).

2. Study Design

This was an uncontrolled, open-label, multicenter, 1-arm study. Efficacy and safety were assessed over the 24-h period following chemotherapy administration to chemotherapy-naive cancer patients that were scheduled to receive cisplatin at the i.v. dose of ≥60 mg/m².

3. Study Population

The study was to be conducted at 5 centers, each expected to contribute six patients for a total of 30 patients.

A summary of the inclusion-exclusion criteria is given in Table 8. In this Table, the reviewer describes in detail the characteristics of the study population in this trial because, since this study was uncontrolled, its results will be compared to those from another trial (historical PL control?). It is very important to establish that, in both studies from which results will be compared, the study populations are similar to each other and that the emetogenic stimulus was standardized.

4. Highlights of Study Execution/Efficacy and Safety Assessments

- At 60 min. before the start of cisplatin therapy, the patient received two Kytril® 1 mg Tablets which he or she swallowed with water. In cases where more than one chemotherapeutic agent was indicated, cisplatin was the first emetogenic agent given.

- On a worksheet, patients recorded the date and time of first nausea, the date and time of the first retching or vomiting, the number of emetic episodes over 24h, the maximum severity of nausea over 24h and the time of first administration of rescue medication within the 24h, if any.

- At 24h after initiation of cisplatin therapy, the coordinator contacted the patient by telephone, and recorded all information on nausea, vomiting and rescue on a source copy of the worksheet. The patient's worksheet was not retained.

- The patients returned to the clinic after approximately 7 days for a follow-up assessment, at which time the AEs and concomitant medications sections of the CRF were updated and female patients received a pregnancy test.

5. Test Medication/Chemotherapy

- Kytril® 1 mg Tablets were supplied in unit-of-use commercial packages of 2 tablets. They were white, triangular, biconvex, film-coated tablets containing 1 mg GRAN free base.[1]

The sponsor provided the following information on compliance. The investigator or pharmacist/oncology nurse signed for the clinical supplies at the time they were received. Records of delivery were reconciled with drug usage records and returned stock. An accounting was required for any discrepancy. Certificates of return were signed to document the return of all unused supplies.

Chemotherapy

The primary chemotherapeutic agent, cisplatin, was administered as an intravenous infusion, 60 min. following the administration of study medication at a dose of at least 60 mg/m², **for no longer than 3h.** No additional cisplatin could be administered during the 24h assessment period. Any other chemotherapeutic agent could be administered concurrently with cisplatin, but cisplatin had to be given first.

- No additional prophylactic antiemetics were permitted during the 24-h assessment period.
  - Patients were allowed an antiemetic rescue medication after a significant degree of nausea or vomiting occurred.
  - "Rescue" medication was defined in this study as a medication indicated for and given specifically to treat nausea and vomiting.
  - Any patient who required antiemetic rescue medication for treatment could receive any antiemetic of the investigator's choosing.
- All patients who received antiemetic rescue medication were to complete the follow-up assessments specified in the protocol and the findings were to be recorded in the CRF.

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[1] The SB lot number and the manufacturing lot number of test medication were:

Study Medication	Strength	Dosage Form	SB Lot Number	Manufacturing Lot Number
Kytril® (BRL43694A)	1 mg	Tablet	X-95209	391180

6. Primary and Secondary Efficacy Parameters

- The primary efficacy variable was the proportion of patients experiencing **Total Control of symptoms** over the 24-h period following initiation of chemotherapy.

  - **Total Control**, a very stringent parameter of efficacy, was defined as no vomiting (or retching), no nausea (any severity), and no rescue medication.

- The secondary efficacy variables assessed during the 24-h period following initiation of chemotherapy were:

  1) **No vomiting**, defined as no vomiting or retching and no use of rescue antiemetics;

  2) **No nausea**, defined as no nausea of any severity and no use of rescue antiemetics;

  3) a third secondary efficacy variable, **Complete Response** (defined as no vomiting or retching, no more than mild nausea, and no rescue antiemetics) was retrospectively added to allow for comparison with data obtained from previously conducted SB studies with GRAN.

7. Statistical Methodology

a. Sample size determination

A sample size of 30 patients [per group] was estimated to result in a 95% confidence interval about the Kytril® Total Control rate of 45% (0.27, 0.63).

b. Comparisons of Interest

- The antiemetic efficacy of Kytril® Tablets 2 mg in Study 436, as assessed by the aforementioned primary and secondary endpoints, was compared with two historical control groups:

  a) patients who received placebo (PL) intravenously in SB Study 012 (PL control),

  NOTE: Study 012 was a single center trial, carried out by Dr. D. Cupissol in France. The aim of the study was to compare I.V. GRAN 40 μg/Kg vs PL as prophylactic agents in chemotherapy-naive patients scheduled to receive cisplatin therapy (≥80 mg/m²) either alone or in combination with other cytostatics. [Reviewed by MO as part of NDA 20-239.]

  and

  b) patients who received oral GRAN 1 mg b.i.d. in SB Study 022 (positive control).

Data obtained during the first 24 hours after chemotherapy with high-dose cisplatin in these three studies (-437 vs -12 and -437 vs -022) were compared.

NOTE: Study /022 used a randomized, D-B, parallel group design and compared three antiemetic regimens: GRAN•HCl, 1 mg b.i.d., orally vs GRAN 1 mg b.i.d., orally plus DEX (12 mg i.v.) vs MCP (7 mg i.v.) + MCP (10 mg t.i.d., given orally) + DEX (12 mg, i.v.). Both comparators in Study 022 are non-approved regimens. [Reviewed by MO as part of NDA 20-305.]

c. Study Populations to be Compared

The sponsor compared the population in Study 436 to that in the two mentioned historical control groups. One comparator was a group of patients who received oral granisetron 1 mg b.i.d. on the day of chemotherapy with high-dose cisplatin; this arm originated from Study 022. The other was a group of patients that originated from Study 012 who received intravenous PL before chemotherapy with high-dose cisplatin.

[The relevance of these comparators is discussed in detail in Section 8. Results, subsection e. Clinical Response, I) Introductory note.]

d. Efficacy Variables

- Point estimates and 95% exact confidence intervals for the primary efficacy variable, **Total Control over 24 h**, and for the secondary efficacy variables [No Vomiting (and no rescue) over 24 hours, No Nausea (and no rescue) over 24 hours, and Complete Response over 24 hours], were generated for the patient population in Study 436. As stated, the results were compared to the values obtained for PL-treated patients in Study 012 and the patients who received oral GRAN 1 mg b.i.d. in Study 022.

- The rates for Total Control, No Vomiting, No Nausea, and Complete Response from each of the three studies were reported as percents, and the confidence intervals about the means were the exact binomials.

- The confidence intervals of the differences in the rates were obtained by the method of normal approximation for the binomial proportions.

e. Levels of significance

For each endpoint, ninety-five percent confidence intervals were generated for the response rate as well as the difference in the response rates between Study 436 and the comparator groups in Studies 012 and 022.

f. Planned efficacy evaluations

- All patients who received medication and received at least one post-dose

assessment made up the intent-to-treat (ITT) population.

- No Protocol-defined analysis was performed.

8. Results

a. Participating Investigators/Patient Accounting

The study was conducted at five centers in the U.S.

- 30 patients completed screening and were enrolled in the trial. Displayed below is the number of patients per center.

Center	Females	Males	Total
1	4	2	6
2	4	5	9
3	0	3	3
4	0	4	4
5	0	8	8
Total	8	22	30

NOTE: According to the FDA statistician, this trial (Protocol 436) seemed to exhibit some treatment allocation issues. For example, Center 2 enrolled patients from #9 to #16 in contiguous patient block, but then enrolled patient #20 instead of #17. Patients #17, 18 and 19 were enrolled at Center 3. Although it is possible that these treatment allocation inconsistencies may have been due to logistical problems, they should have been addressed by the sponsor.

b. Protocol violators (n=7)

These are listed below. Although these are listed here, no protocol-defined analysis was planned or done (only ITT analysis).

- Patient 436.005.0036 took MTX 23h prior to Time 0.

- Patients 436.001.0001, 436.001.0002 and 436.001.0005 took Decadron ca. 12h prior to Time 0.

- Patient 436.004.0027 did not record vomiting information for the 24 hour-period prior to Time 0.

- Two patients had cisplatin infusion lasting for more than 3h. One (436.005.0035) had cisplatin infused for a total period of 3h and 22 min. Another (436.005.0037) had cisplatin infused for a total period of 3h and 45 min.

c. Patient demographics/baseline disease characteristics (Table 9)

In this Table, the reviewer presents very detailed information on demographics and baseline disease characteristics. Only 8 of the 30 patients were female,

and the ratio F/M in this study was 0.4. This F/M ratio is very different from the 2.5 observed in Study -215. Most patients were Caucasian, of mean age of 68.5y and mean body weight of 162 pounds. The primary malignant neoplasms were respiratory/intrathoracic (53.3%) and of the digestive organs (20%), followed by genitourinary (16.7%) and other sites (10%). Twenty-five of the 30 patients (83.4%) had Karnofsky scale of 80 or higher[2], Eighty-three percent of the patients had signs, symptoms and ill-defined conditions; 53.3 per cent had circulatory system problems. The primary chemotherapeutic agent used in Study 436 was cisplatin (100% of the patients), at a moderately high emetogenic dose (77.6 mg/m^2), followed by a variety of chemotherapeutic agents administered at doses that had moderate emetogenic potential.

d. Use of additional antiemetic medication (Table 10)

- 25/30 (83.3%) of the patients took additional antiemetics over the entire study period (from screening to follow-up).
- The most frequently administered additional antiemetic was prochlorperazine, given to 22 (73.3%) patients.
    - The next most commonly used agents were DEX (9 patients or 30%), GRAN•HCl (8 patients or 26.7%), OND•HCl and diphenhydramine•HCl (4 patients each or 13.3% each), and lorazepam (3 patients or 10%).
- 16 of the 30 patients took additional antiemetic medication during the assessment period, but only 7 patients used them according to protocol guidelines.[3]
    - 8 patients used antiemetic rescue for mild nausea without vomiting; and one patient, for anxiety in anticipation of nausea.
    - Thus, 9 (30%) of the patients used additional antiemetics inappropriately.

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[2] Karnosky Scale

100	Normal, no complaints, no evidence of disease	(16.7%)
90	Able to carry on normal activity, minor signs or symptoms of disease	(46.7%)
80	Normal activity with effort, some signs of symptoms of disease	(20.0%)
70	Cares for self. Unable to carry on normal activity or to do active work	(16.7%)

[3] These guidelines stipulated that additional antiemetics should be used only after experiencing a significant degree of nausea or vomiting during the 24-h assessment period.

TABLE 9
Study -436

Demographic and Baseline Disease Characteristics

		n 30	% 100
A. Demographics			
Gender	Male	22	73.3
	Female	8	26.7
Mean Age (y)		68.5	
Range (y)			
Race	Caucasian	28	93.3
	Black	1	3.3
	Oriental	1	3.3
Mean Body Weight (lbs.)		162	
B. Primary Disease Site			
Malignant Neoplasm	• Respiratory/Intrathoracic	16	53.3
	• Digestive Organ	6	20.0
	• Genitourinary	5	16.7
	• Other Sites	3	10.0
Karnofsky Scale	100	5	16.7
	90	14	46.7
	80	6	20.0
	70	5	16.7
C. Other Significant Presenting Conditions			
Signs, Symptoms and Ill-defined Conditions		25	83.3
Circulatory System		16	53.3
Musculoskeletal System		12	40.0
Digestive System		11	36.7
Respiratory System		10	33.3
D. Chemotherapeutic Agents			
Cisplatin		30	100.0
Etoposide		8	26.7
Vinblastine-SO_4		7	23.3
Mitomycin		6	20.0
5-FU		5	16.7
Taxol		5	16.7
Doxorubicin		4	13.3
Cyclophosphamide		1	3.3
MTX		1	3.3
Vinorelbine Ditartrate		1	3.3
Folinic Acid		1	3.3
Mean Cisplatin Total Dose (mg/m^2)		77.6 [Min.=60.0; Max.=100.5]	
E. Prior Medications			
CNS agents (analgesics)		10	33.3
Alimentary Tract/Metabolism		4	13.3

TABLE 10
Study -436

Proportion of Patients Who Used Additional Antiemetic Medications by Study Period

Time Period	Patients in Study 436 (n=30) n (%)
Entire Study Period	**25 (83.3)**
24-hour assessment period	**16 (53.0)**
- Rescue[a] for Mild Nausea Only	8 (26.6)
- Rescue for Mild Nausea and Vomiting	2 (6.6)
- Rescue for Moderate to Severe Nausea and Vomiting	5 (17.0)
- Additional antiemetics taken for Other Reasons (Anxiety)	1 (3.3)
From the end of the 24-hour assessment period to end of follow-up	9 (30.0)

a) Rescue medication was defined as that medication ***given specifically*** *to treat nausea or vomiting.*

e. Clinical response

i) Introductory Note: Validity of Comparators

The sponsor proposes to demonstrate efficacy via a comparison of results from Study -436 to two historical controls: 1) patients who received intravenous PL in the SB Study -012 (historical PL); 2) patients who received oral GRAN 1 mg b.i.d. in SB Study -022 (positive historical control). Data from both studies were previously assessed by the Medical Officer, in reviews dated January 13, 1993 and January 12, 1994, respectively. Thus, a first order of business is to establish whether the proposed comparator groups, one negative, the other positive, are relevant. This is done by establishing comparability in many respects. This includes comparisons of the study populations in terms of demographics, primary cancer types, and assessing whether there was standardization of the emetogenic stimulus and whether the latter can be categorized as "high dose cisplatin". Significant protocol violations and any other factor that may influence response also are important to compare.

From the data displayed in Table 11 and from previous appraisal of these data it seems that aside of the mean cisplatin dose, the comparators proposed by the sponsor may not be relevant. Reasons for this constraint include:

TABLE 11
Study -436

Design, Demographics, Primary Cancer Types and Emetogenic Stimulus in Study 436 and the Sponsor's Proposed Comparator Groups Originating from Study 012 and 022

	Study 436 Two 1 mg Kytril® Tablets, Once	Study 012 PL i.v. 5 min. infusion	Study 022 Oral GRAN 1 mg b.i.d.
Number of Patients	30	14	119
Parameter	n (%)	n (%)	n (%)
Design	1-arm, uncontrolled, open-label, multicenter	2-arm, single center, double-blind, randomized parallel group	3-arm, randomized, double-blind, parallel group
Gender Females Males	8 (26.7) 22 (73.3)	6 (42.9) 8 (57.1)	71 (59.7) 48 (40.3)
F/M Ratio	0.36	0.75	1.48
Mean Age (y)	68.5	61.1	54.9
Race White Black Oriental	28 (93.3) 1 (3.3) 1 (3.3)	14 (100) 0 0	92 (77.3) 23 (19.3) 4 (3.4)
Mean B_{WT} (lbs.)	162	142	143
Primary Cancer Types	Respiration/ Intrathoracic 16 (53.3) Digestive Organ 6 (20.0) Genitourinary 5 (16.7) Other 3 (10.0)	Head and Neck 4 (28.6) Ovary 3 (21.4) Lung 3 (21.4) Esophagus 2 (14.3) Uterus 2 (14.3)	Ovary 26 (21.8) Cervix 27 (22.7) Head and Neck 20 (16.8) Lung 10 (8.4) Urethra/Bladd. 11 (9.2) Stomach 9 (7.6) Esophagus 5 (4.2)
Mean Cisplatin Dose mg/m² [Range]	77.6	80.5	80.0

a) Sample size considerations [14, the n in Study 012 is one-half that of 30 in Study -436; the n in Study 022 (119) is, in turn, four times larger than 30].

b) The fact that study 012 was a single center trial in a small group of patients. Although ethical considerations may most certainly be invoked, study 012 cannot be considered of great value.

c) An important difference is the ratio of female to male patients. This ratio is very different in the three trials.

Gender of the patient is one of the factors affecting the incidence of N&V after cancer therapy. More females experience

N&V than males; also, N&V is more severe in females than males. In addition, antiemetics are more effective in males than females. The following data with GRAN•HCl are presented in support of this statement.

- The 24-h Complete Response for the GRAN 1 mg b.i.d. only arm in Study 022 was:

Complete Response		
Females	Males	Total
27/71 (38%)	35/48 (73%)	62/119 (52%)

This gender-dependent response was also shown in the other arm (MCP-DEX) of Study 022:

Complete Response		
Females	Males	Total
34/76 (45%)	29/45 (64%)	63/121 (52%)

as well as in the GRAN•HCl i.v. (40 μg/Kg) arm of Study 003:

Complete Response		
Females	Males	Total
21/44 (48%)	79/99 (80%)	100/143 (70%)

and the MCP-DEX arm of Study 003:

Complete Response		
Females	Males	Total
30/54 (56%)	63/84 (75%)	93/138 (67%)

Furthermore, the reader is reminded of the results in Study 215, reviewed above. As shown in Table 7b, for all parameters of efficacy, response in males was - at least numerically - always higher than in females.

Therefore, with GRAN and comparator arms, a higher Complete Response and other efficacy parameters in males is consistently shown [and expected].

d) The difference in average age between patients in Study 436 and Study 022. This difference was 13.6y, which may be clinically important.

- The importance of this imbalance is due to the fact that another factor known to influence chemotherapy-induced emesis is **age**. Younger patients experience more N&V than older patients. The following data, taken from Study 022, illustrates the age-dependent response in all three arms of this trial.

Complete Responders by Age

Age Group (y)	GRAN [n=118]	GRAN-DEX [n=117]	MCP-DEX [n=121]
45 to <65	54%	59%	51%
≥65	65%	71%	81%
(Δ)	(11%)	(12%)	(30%)

e) On the average, patients in Study 436 were 19 lbs. heavier than those in Study 022 and 20 lbs. heavier than those in Study 012. It is not known if this imbalance in weight among the groups being compared has an influence in response.

f) Differences are also seen among the three studies in the primary cancer types. Again, it is not known if these imbalances may affect response (more on this factor under Additional Comments).

It seems necessary to check out the impact of these imbalances through statistical analyses. On the other hand, the three groups of patients (Table 11) appeared to be balanced in regard to a very important parameter: the emetogenic stimulus. The latter was cisplatin-based, ca. 80 mg/m² for each of the three groups.

It is important to keep all of the above listed constraints in mind when assessing efficacy via the sponsor's proposed approach. The reviewer maintains that the comparison of results from Study -436 to those in the PL arm of Study 012 and in the 1 mg b.i.d. arm of Study 022 is not valid. This is because the three groups being compared differ in many factors that matter.

ii) Results of efficacy analyses
(Sponsor's evaluations)

- Table 12 (modified and expanded from sponsor's presentation of data) gives a summary of the results obtained for the four efficacy parameters in Study 436 and the two comparators. As shown in the last two columns of this Table (% Δ), the therapeutic gain with the 2 mg u.i.d. (Study

436) over intravenous PL appeared to be clinically meaningful: 23% for total control and 30% or more for the other three parameters. These results are to be contrasted to those from the comparisons of 2 mg u.i.d. with the 1 mg b.i.d. which **went in the opposite direction**: 14% less total control, 15% less Complete Response, 19% less NO vomiting and 5% less NO nausea.

- The % Δs displayed in Table 12 suggest (but do not prove) that the 2 mg u.i.d. dose regimen in Study 436 may be a) superior to intravenous PL but b) not necessarily bioequivalent to 1 mg b.i.d. The sponsor claimed to demonstrate superiority over one comparator and bioequivalence to the other, through statistical analyses comparing the 95% C.I. the difference in mean results.

TABLE 12
Study -436

Summary of Efficacy Analyses. Percent of Responders and 95% Confidence Intervals in Study 436 and the Comparator Groups for Total Control, Complete Response, No Vomiting and No Nausea

	Study 436 [n=30] % Responders (95% C.I.)	Study 012 [n=14] % Responders (95% C.I.)	Study 022 [n=119] % Responders (95% C.I.)	% Δ	
Parameter				2 mg u.i.d. vs PL	2 mg u.i.d. vs 1 mg b.i.d.
Total Control	30 (11.9, 48.1)	7 (0.2, 33.9)	44 (34.7, 53.0)	+23%	-14%
Complete Response	37 (17.8, 55.6)	7 (0.2, 33.9)	52 (42.7, 61.5)	+30%	-15%
No Vomiting	37 (17.8, 55.6)	7 (0.2, 33.9)	56 (47.0, 65.6)	+30%	-19%
No Nausea	40 (20.8, 59.2)	7 (0.2, 33.9)	45 (35.2, 53.9)	+33%	- 5%

- Regarding their approach, the sponsor noted:

  - If the 95% C.I. around the difference in mean results **does not include zero**, then the difference <u>is statistically significant</u>.

  - If the 95% C.I. around the difference in mean results **does include zero**, then the difference <u>is not statistically significant</u>.

- The results of the sponsor's statistical analyses are summarized in Table 13. The reader's attention is directed at the last two columns of this Table (added by the reviewer).

  - Based on the sponsor's analysis, the trial indicates effectiveness of the 2 mg u.i.d. regimen in comparison to the selected

historical PL. However, according to evaluations by Dr. M. Huque, FDA biometrician, the results were driven mainly by the female subgroup. This important observation is illustrated in Tables 14 and 15, modified by the MO from Dr. Huque's review of July 31, 1996.

TABLE 13
Study -436

Efficacy Parameters: Summary of Statistical Analyses
(Sponsor's Approach)

Study # (Number of Patients)	Responders % (95% C.I.)	C.I. of Difference[a] vs Study 436		
		C.I.	Includes Zero	Statistical Significance
TOTAL CONTROL				
436 (n=30)	30 (11.9, 48.1)			
012 (n=14	7 (0.2, 33.9)	0.49, 45.23	NO	YES
022 (n=119)	44 (34.7, 53.0)	-32.70, 5.30	YES	NO
COMPLETE RESPONSE				
436 (n=30)	37 (17.8, 55.6)			
012 (n=14)	7 (0.2, 33.9)	6.49, 52.56	NO	YES
022 (n=119)	52 (42.7, 61.5)	-35.21, 4.34	YES	NO
NO VOMITING				
436 (n=30)	37 (17.8, 55.6)			
012 (n=14)	7 (0.2, 33.9)	6.49, 52.56	NO	YES
022 (n=119)	56 (47.0, 65.6)	-39.38, 0.11	YES	NO
NO NAUSEA				
436 (n=30)	40 (20.8, 59.2)			
012 (n=14)	7 (0.2, 33.9)	9.60, 56.11	NO	YES
022 (n=119)	45 (35.2, 53.9)	-24.55, 15.47	YES	NO

a) 95% Confidence Interval of normal approximation to binomial proportions.

- As shown in Table 14, the number of patients per center is small. Indeed, centers #3, 4 and 5 did not enroll any female patients. This makes it difficult to draw meaningful conclusions.

  - Nonetheless, the observed success rate with respect to the total control of symptoms was **45% higher in females** (63%) than in males (18%)!!!

- Similarly, with respect to the parameter Complete Response, the response in females (63%) was 36% higher than in males (27%).

TABLE 14
Study -436

Proportion of Patients with Total Control [TC (Primary Endpoint)] and Complete Response [CR] by Center and Gender

Center	Females		Males		Total			
	TC	CR	TC	CR	TC		CR	
1	3/4	3/4	0/2	0/2	3/6	(50%)	3/6	(50%)
2	2/4	2/4	2/5	2/5	4/9	(44%)	4/9	(44%)
3	0/0	0/0	0/3	0/3	0/3	(0%)	0/3	(0%)
4	0/0	0/0	1/4	1/4	1/4	(25%)	1/4	(25%)
5	0/0	0/0	1/8	3/8	1/8	(13%)	3/8	(36%)
Pooled	5/8 (63%)	5/8 (63%)	4/22 (18%)	6/22 (27%)	9/30 (30%)		11/30 (37%)	

NOTE: This Table corresponds to Table 7 in Dr. M. Huque's Statistical Review and Evaluation of July 31, 1996, with some modifications.

- In addition, the FDA Biometrician presented results of a statistical comparison of the success rates (total control and complete response) for male patients for GRAN 2 mg u.i.d. versus the historical PL control. Results of these evaluations are summarized in Table 15. As seen in the last column of this Table, for both TC and CR, the response in females in Study 436 (63%) was superior to the PL response in Study 012 (0%). However, neither for TC nor for CR, the success rates in males (11% and 27%, respectively) were statistically different from those observed with the PL historical control. It is therefore concluded that the overall results ("combined") were driven mainly by the female subgroup. Such results are inconsistent with the so many previous observations documented by the MO above (where the response in male was higher than in female patients).

TABLE 15
Study -436

Comparison of the Success (Response) Rates for Males
(GRAN 2 mg Once Daily vs the Historical PL Control)

Gender	Endpoint	GRAN 2 mg once-a-day (Protocol 436)	Historical PL (Protocol 012)	Δ	2-Sided p-value[a] Exact	Asymptotic
Females	TC	5/8 (63%)	0/6 (0%)	63%	0.031	--
	CR	5/8 (63%)	0/6 (0%)	63%	0.031	--
Males	TC	4/22 (18%)	1/8 (13%)	5%	N.S.	N.S.
	CR	6/22 (27%)	1/8 (13%)	12%	N.S.	N.S.
Combined	TC	9/30 (30%)	1/14 (7%)	23%	N.S.	0.035
	CR	11/30 (37%)	1/14 (7%)	30%	N.S.	0.008

a) For females, by Fisher's Exact. For others, difference in proportions method using StatXact software.

NOTE: This Table corresponds to Table 8 in Dr. M. Huque's Statistical Review and Evaluation (July 31, 1996), with some modifications.

- As previously mentioned, the design of trial 436 is not really adequate for establishing clinical equivalence between the proposed 2 mg u.i.d. dose regimen and the approved 1 mg b.i.d. regimen derived from Study 022 due to a number of reasons. The primary consideration for this concern is the substantial difference in **sample size (n=30 vs 119)**. According to the rules set up by the sponsor, there were no statistically significant differences for any of the efficacy parameters when comparing 2 mg u.i.d. (Study 436) to those of the historical control of oral GRAN 1 mg b.i.d. (originating from Study 022). However, as depicted in Table 13, the 95% C.I. for <u>all</u> efficacy endpoints were wide and way beyond the ± 10% limits set for establishing clinical equivalence. It is therefore concluded that trial 436 **did not provide a statistical evidence of clinical equivalence** between the newly proposed 2 mg once-a-day GRAN regimen and the approved dose regimen (1 mg b.i.d.) of the drug.

f. <u>Results of safety evaluations</u>

- In this trial 28/30 (93%) of the patients experienced at least one AE. The most frequently reported AEs (>5%), per body system classification were digestive system (80%), body as a whole (60%) and nervous system (20%).

- The most commonly reported AE was nausea[4] (53% of the patients), followed by asthenia 37%), vomiting (37%), headache (17%), ↓ appetite (13%), diarrhea (13%), constipation, fever and leukopenia (10% each).

- The majority (22 of 30 = 73%) of AEs reported were mild in severity. Six (20%) of the patients reported severe AEs, the most common of which were *vomiting* (3 patients or 10%), nausea (2 patients or 7%), and asthenia (2 patients or 7%). The majority (93%) of AEs were considered not related to test medication by the investigator-determined relationship.

- Neither serious AE (6 pts. reported a total of 16 SAEs during the course of the study or within 30 days of receiving test med.) nor deaths (n=3 within 30 days of receiving test med.) were considered related to test med.

- No pt. was W/D from the trial due to an AE.

9. <u>Conclusions (Sponsor)</u>

The sponsor concludes that "These observations support the antiemetic efficacy of Kytril® Tablets as a single 2 mg dose, when compared with the response of PL-treated patients".

[4] However, nausea was an efficacy endpoint and all occurrences of nausea during the 24-h assessment period were not considered AEs. When this was taken into account and a correction was applied, the number of patients reporting nausea as an AE was 7 (23%).

"These analyses also indicate that a single dose of 2 mg provided comparable efficacy to the regimen of 1 mg taken twice on the day of chemotherapy, as seen in the comparisons of the results of Study 436 with the response rates in patients treated with oral granisetron in study 022".

10. Reviewer's Additional Comments

Study 436 is the second trial which results have been submitted in support of the approval of GRAN, 2 mg once-a-day dose regimen as an alternate to the approved 1 mg b.i.d. dose regimen. The study was uncontrolled (one-arm), open-label. So, to demonstrate efficacy, comparisons to historical data are needed. The sponsor attempted to demonstrate efficacy by comparing the results of this trial to a) those in Study 012 (PL response after intravenous 5-min. infusion) and b) those results with the 1 mg b.i.d. arm originating from Study 022. But, as shown in utmost detail in the text of the review of Study 436, except for degree of cisplatin emetogenicity, neither comparator appears to be valid.

In addition to the reasons already discussed, Study 022 **per se**, had not show that the 1 mg GRAN b.i.d. chosen by the sponsor, was active. This was because this trial included neither PL nor a low dose of GRAN to serve as internal comparators. Actually, Study 022 was the main reason not to initially recommend approval of oral GRAN (MO review of January 12, 1994). As pointed out in memorandum from Dr. S. Fredd, the Division Director, to NDA 20-305, March 4, 1994, "Study 022 was not adequate to support effectiveness. A post-hoc historically controlled method was invoked by the sponsor to provide evidence for 24-h control (the study was conceived as a 7-day study, not a 24-h trial). But with this approach, an assertion of efficacy at a 99% confidence interval was not supported".

Besides the many enumerated constraints when using historical comparators, listed in detail within the text of this review, the statistical analyses did not provide reasonable evidence of effectiveness of the 2 mg once-a-day dose regimen of GRAN. According to the FDA biometrician evaluations, Study 436 failed to provide a statistical evidence of clinical equivalence between the 2 mg u.i.d. and the approved 1 mg b.i.d. dose regimens of GRAN because the 95% C.I. for all efficacy endpoints were wide and way beyond the ± 10% limits set for establishing clinical equivalence. Moreover, although Study 436 indicated effectiveness of the 2 mg u.i.d. GRAN dose regimen in comparison to the historical PL selected by the sponsor, these results must be interpreted in the context of other facts. There was a significant gender effect, which was inconsistent with previous results with GRAN and comparators. In Study 436, the results were driven primarily by the female subgroup. The response rates in males for the 2 mg once-a-day GRAN regimen were **PL-like**: only 2/22 (18%) for "total control" and 6/22 (27%) for "complete response".

The overall conclusion is that Study 436 **is not adequate**. This study supports neither effectiveness nor clinical bioequivalence. It does not replicate the "bioequivalence" findings in Study 215.

V. OVERALL CONCLUSIONS

- Study 215 was a well-designed and well-executed randomized trial in cancer patients receiving mainly non-cisplatin-based chemotherapy regimens of moderate emetogenic potential. This trial, in a large number of patients, appears to show that GRAN 2 mg once-a-day is equivalent to GRAN 1 mg b.i.d. But comparisons to two **relevant** historical controls - GRAN 0.25 mg b.i.d., originating from Study 021 and PCPZ, 10 mg b.i.d., originating from Study 288 (both trials, 021 and 288 were pivotal for the approval of the GRAN 1 mg b.i.d. regimen) - do not support effectiveness.

- Study 436, an open-label study in a small number of cancer patients receiving cisplatin at doses of moderately high emetogenic potential was not adequate. This trial supports neither effectiveness nor clinical equivalence.

VI. RECOMMENDATIONS FOR REGULATORY ACTIONS

On the basis of the evidence at hand (Study 215 and Study 436), the reviewer does not recommend approval of the new 2 mg once-a-day regimen of granisetron as an alternate to the approved 1 mg b.i.d. regimen.

1. Although, in Study 215, the 2 mg u.i.d. GRAN regimen appears to be bioequivalent to the GRAN 1 mg regimen, no evidence has been presented that either arm is active. So, the demonstration of bioequivalence is not convincing.

   In addition, the Complete Response values in Study 215 are quite low. The sponsor should be asked if the results for Complete Response have been checked. Could this be Total instead of Complete Response?

2. In Study 436 no activity has been demonstrated since comparisons to results with historical i.v. placebo do not show statistically significant difference. Furthermore, comparisons to 1 mg b.i.d. GRAN (historical control) do not support clinical equivalence. Study 436 supports neither effectiveness nor equivalence.

October 10, 1996

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-305/S-001
HFD-180
HFD-180/SFredd
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
r/d 9/6/96 jgw
f/t 10/9/96 jgw
MED\N\20305609.0HG

10/10/96

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020305 (S001)

STATISTICAL REVIEW(S)

STATISTICAL REVIEW & EVALUATION
NDA/Supplement

April 14, 1997

NDA #20-305/Supplement #001
Sponsor: *SmithKline Beecham*
Drug: *(granisetron hydrochloride) Kytril*[R]
Indication: *prevention of nausea and vomiting in emetogenic cancer therapy patients*
Documents Reviewed: Sponsor's re-submissions February 20, 1997
Medical officer: Dr. Gallo--Torres

BACKGROUND

Statistical review of July 25, 1996, of this NDA supplement indicated the following deficiencies:

- For Study 215, the 2 mg daily dose appeared to be clinically equivalent to the 1 mg twice daily dose for complete response and for no nausea, but no data was provided to demonstrate that the control treatment was active in the trial.

- The 2 mg daily dose was compared to a historical control in a trial, but did not establish its effectiveness.

In the current re-submission of February 20, 1997, the sponsor does the following:

(1) Granisetron treatment groups of Study 215 are compared to the prochlorperazine group (historical control) of Study 288 to validate that the active treatments of Study 215 are effective in the trial.

(2) To further substantiate the efficacy of granisetron 2 mg once daily regimen, the sponsor submitted a report of Study 402, in which "moderately" emetogenic agents were given. The primary objective in Study 402 was to compare the efficacy of 2 mg once daily, given orally, with that of 32 mg intravenous (iv) ondansetron. Concomitant prophylaxis dexamethasone was permitted in the study. Granisetron 2 mg once a day treated patients who did not receive prophylaxis dexamethasone are compared to the prochlorperazine historical control of Study 288.

(3) To address the efficacy of a single 2 mg dose of granisetron in high dose cisplatin patients, the sponsor submitted a report of Study 341. The primary objective in this study, like Study 402, was to compare efficacy of 2 mg once daily dose regimen to 32 mg iv ondansetron.

Concomitant prophylaxis dexamethasone was permitted in the study. The subgroup of patients who did not receive prophylaxis dexamethasone are compared to placebo from Study 012 (historical control) and to the granisetron 1 mg bid treated group from Study 022 (historical positive control).

STUDY #215

Study Design

This was a double-blind, randomized, parallel group study to compare the efficacy and safety of a new dose regimen of granisetron to an approved dose regimen of granisetron in preventing acute nausea and emesis over a 24-hour period in patients receiving moderately emetogenic chemotherapy. The target patient population was adult males and females naive to chemo-therapy, but scheduled to receive moderately emetogenic chemotherapy for malignant disease.

Patients were screened within one week of their scheduled chemotherapy, and were stratified by gender and were randomized to receive either 1 mg oral granisetron bid or 2 mg once a day granisetron. To maintain double-blind, each patient received 2 tablets (either 1 active 1 matched placebo, or 2 active depending on the randomized treatment) one hour prior to chemotherapy. A second dose of study medication (either 1 tablet active and 1 placebo, or two tablets placebo) was to be taken by the patient 12 hours after the first dose. Patients were retained at the clinic for at least 1 hour after chemotherapy. They were then dispensed study medication to be taken at home for the 12 hour administration. Patients were to record on a "patient-worksheet"diary nausea and emesis information at 6 hour intervals for the 24-hour period following chemotherapy.

After completing the double-blind portion of the study (cycle #1), patients were given the option to continue in an open label manner on granisetron 2 mg once a day treatment for the subsequent chemotherapy treatment cycles.

The planned primary endpoint was the proportion of patients with complete response defined as having no nausea, no emesis, and no rescue administration during the first 24 hour period (first cycle). Other primary endpoints considered for the first 24-hour period were: the proportion of patients with no emesis, and the proportion of patients with no nausea. The secondary endpoints considered for the first 24-hour period were: frequency of emesis, frequency and maximum severity of nausea, and the incidence of rescue medication.

The trial was planned to establish clinical equivalence to detect a treatment difference of 10 percent in between treatment response rates with 80% power and $\alpha = .05$ with a two-sided alternative hypothesis, on assuming an average response rate of 75 percent. Statistical analyses were planned only for the primary endpoints. The planned analyses were to provide p-values

by the Mantel-Haenszel test (M-H test) and the 95% confidence intervals results by the intention-to-treat and per-protocol methods.

Sponsor's Old Analyses and Efficacy Results

A total of 700 patients were randomized, 356 to granisetron 1 mg bid (active control), and 344 to granisetron 2 mg once a day regimen. A total of 672 patients completed cycle-1 (randomized DB-period), 341 for active control and 331 for the granisetron 2 mg once a day regimen. The remaining 700-672=28 patients discontinued from the trial for various reasons. Other details are given in the in the statistical report of July 25, 1996. Tables 1 and 2 show the sponsor's primary efficacy results by the intention-to-treat and by the protocol defined methods.

Table 1
Sponsor's Results for the Primary Endpoints, First 24-Hours (Cycle-1)
(Intention-To-Treat Population)

Stratum	Endpoint	granisetron 1 mg bid	granisetron 2 mg once a day	Difference % (95% CI)	P-value (M-H test)
female	Complete R.	115/252 (46%)	116/245 (47%)	-1.7 (-10.5, 7.1)	.702
	No emesis	200/252 (79%)	182/245 (74%)	5.1 (-2.3, 12.5)	.180
	No nausea	118/252 (47%)	120/245 (49%)	-2.2 (-10.9, 6.6)	.631
male	Complete R.	64/102 (63%)	57/98 (58%)	4.6 (-9.0, 18.1)	.509
	No emesis	90/102 (88%)	81/98 (83%)	5.6 (-4.2, 15.3)	.264
	No nausea	64/102 (63%)	60/98 (61%)	1.5 (-11.9, 15.0)	.825
combined	**Complete R**	**179/354 (51%)**	**173/343 (50%)**	**0.1 (-7.3, 7.6)**	**.908**
	No emesis	290/354 (82%)	263/343 (77%)	5.2 (-0.8, 11.3)	.088
	No nausea	182/354 (51%)	180/343 (53%)	-1.1 (-8.5, 6.4)	.770

Table 2
Sponsor's Results for the Primary Endpoints, First 24-Hours (Cycle-1)
(Protocol Defined Population)

Stratum	Endpoint	granisetron 1 mg bid	granisetron 2 mg once a day	Difference % (95% CI)	P-value (M-H test)
female	Complete R.	101/228 (44%)	103/223 (46%)	-1.9 (-11.1, 7.3)	.687
	No emesis	182/228 (80%)	166/223 (74%)	5.4 (-2.4, 13.1)	.174
	No nausea	104/228 (46%)	107/223 (48%)	-2.4 (-11.6, 6.8)	.615
male	Complete R.	51/86 (59%)	48/83 (58%)	1.5 (-13.4, 16.3)	.847
	No emesis	76/86 (88%)	69/83 (83%)	5.2 (-5.3, 15.8)	.331
	No nausea	51/86 (59%)	50/83 (60%)	-0.9 (-15.7, 13.8)	.901
combined	**Complete R**	**152/314 (48%)**	**151/306 (49%)**	**-0.9 (-8.8, 6.9)**	**.807**
	No emesis	258/314 (82%)	235/306 (77%)	5.4 (-1.0, 11.7)	.098
	No nausea	155/314 (49%)	157/306 (51%)	-1.9 (-9.8, 5.9)	.621

Sponsor's New Analyses and Results/ Study 215

In the new analysis the sponsor compared granisetron treatment groups of Study 215 to the prochlorperazine group (historical control) of study 288 to validate that the active treatments of Study 215 were effective in the trial. In this comparison the sponsor included 356 patients who received granisetron 1 mg bid and 344 patients who received 2 mg once daily from Study 215, and 111 prochloroperazine patients from Study 288. Study 288 was submitted to the original NDA on June 15, 1994, and the results of the study are contained in the approved prescribing information.

The treatment groups compared exhibited no noticeable differences with respect to demographic characteristics except that the historical control had about 13% more females (Table 3).

Table 3
Demographic comparisons:
granisetron treated groups (Study 215) versus historical control (Study 288)

Demographic Characteristic	Study 215 granisetron 1 mg bid N=356	Study 215 granisetron 2 mg once daily N=344	Study 288 prochlorperazine 10 mg bid N=111
Gender:			
Male	103 (29%)	98 (29%)	18 (16%)
Female	253 (71%)	246 (72%)	93 (84%)
Mean Age (years)	55.3	56.0	59.3
Race:			
Black	43 (12%)	41 (12%)	13 (12%)
Caucasian	293 (82%)	291 (85%)	90 (81%)
Other	10 (6%)	12 (3%)	8 (7%)
Weekly Alcohol Consumption*	3.6	4.7	2.4

* 1 unit=150 ml wine, or 0.25 L beer, or 50 ml of spirits.

Table 4 shows a frequency distribution by most common site of disease and by most common primary malignancies for the treatment groups compared. Table 5 shows similar comparison by chemotherapeutic agents, and Table 6 summarizes efficacy comparison results.

Table 4
Comparison by most common site of disease and malignancies: granisetron treated groups (Study 215) versus historical control (Study 288)

most common site of disease and malignancies	Study 215 granisetron 1 mg bid N=356	Study 215 granisetron 2 mg once daily N=344	Study 288 prochlorperazine 10 mg bid N=111
Breast Cancer	49.7%	50.1%	62.2%
lymphoma	15.7%	13.7%	7.2%
Lung	12.1%	14.3%	15.3%

Table 5
Comparison by most common chemotherapeutic agents (> 10%) administered: granisetron treated groups (Study 215) versus historical control (Study 288)

Demographic Characteristic	Study 215 granisetron 1 mg bid N=356	Study 215 granisetron 2 mg once daily N=344	Study 288 prochlorperazine 10 mg bid N=111
Cyclophosphamide	258 (73%)	258 (75%)	90 (81%)
Doxorubicin	174 (49%)	179 (52%)	43 (39%)
Fluorouracil	137 (39%)	134 (39%)	60 (54%)
Carboplatin	62 (17%)	52 (15%)	22 (32%)
Methotrexate	58 (16%)	58 (17%)	36 (32%)
Etoposide	47 (13%)	46 (13%)	36 (32%)
Vincristine	40 (11%)	52 (15%)	12 (11%)
Cisplatin	40 (11%)	44 (13%)	-

Table 6
Efficacy results at 24 hours
granisetron treated groups of Study 215 versus prochlorperazine of Study 288

Efficacy Endpoints	Study 215 granisetron 1 mg bid N=356	Study 215 granisetron 2 mg once daily N=344	*Study 288 prochlor-perazine 10 mg bid N=111	95% CI 1 mg bid vs. Historical Control	95% CI 2 mg once vs. Historical Control
Complete Response	69.8%	64.0%	41.4%	17.0% to 37.8%	12.0% to 33.0%
No vomiting	81.9%	76.5%	48.2%	23.6% to 43.9%	18.1% to 38.9%
No nausea	51.4%	52.5%	35.1%	5.95% to 26.6%	6.98% to 27.7%
Total control	50.6%	50.4%	33.3%	7.0% to 27.5%	6.8% to 27.4%

* Historical control

Reviewer's Comments/Study 215

Tables 4 and 5 show some differences between the granisetron treated groups of Study 215 and the historical control prochlorperazine of Study 288. However, all the differences are within 15%. Therefore, given the sample size of 111 of the historical control, these differences will either be not significant or at most borderline significant at the .05 level.
Hence, given the size of the effect and the above comparability results of the patient characteristics, this reviewer is satisfied about the adequacy of the above historical control comparisons. The size of the effect in comparison to the historical control is convincing in that the lower 95% confidence intervals are consistently well above zero.

Therefore, the results of Study 215 suggest that the 2 mg once a day dose regimen is clinically not worse than the already approved 1 mg bid dose for the given indication.

SUPPORTIVE EVIDENCE FROM STUDY 402

Study 402, completed in April 1996, was designed to compare the efficacy of a single oral dose of granisetron (2 mg) with the efficacy of a single intravenous dose of ondansetron (32 mg) , given once before chemotherapy, in preventing acute nausea and emesis in patients with malignant disease receiving cyclophosphamide or carboplatin based chemotherapy. The study was double blind, multicenter, of parallel group design in which a total of 1085 patients were

randomized, 542 receiving granisetron, and 543 receiving ondansetron. It involved a total of 106 investigators from U.S., Puerto and Canada. The use of prophylactic dexamethasone or methylprednisone was permitted in the trial and patients were stratified to treatment by their use or non-use of corticosteroids.

This study included a sub-group of 101 gransetron (2 mg once daily) treated patients who did not receive corticosteroids. This sub-group is compare to a historical control prochlorperazine 10 mg bid of Study 288. The results claimed for this sub-group historical control analysis are as follows:

Table 7
Demographic comparisons:
granisetron 2 mg once a day sub-group (data from Study 402) versus historical control prochlorperazine of Study 288

Demographic Characteristic	granisetron 2 mg once daily sub-group from Study 402 N=101	Study 288 prochlorperazine 10 mg bid N=111
Gender:		
Male	30 (30%)	18 (16%)
Female	71 (70%)	93 (84%)
Mean Age (years)	55.3	59.3
Race:		
Black	14 (14%)	13 (12%)
Caucasian	76 (75%)	90 (81%)
Other	11 (11%)	8 (7%)

APPEARS THIS WAY
ON ORIGINAL

Table 8
Comparative Efficacy results at 24 hours
granisetron 2 mg once a day sub-group data from Study 402 versus historical control prochlorperazine of Study 288

Efficacy Endpoints	granisetron 2 mg once daily sub-group from Study 402 N=101	*Study 288 prochlorperazine 10 mg bid N=111	95% CI for the absolute difference
Complete Response	58.4%	41.4%	**3.61%, 30.33%**
No vomiting	79.2%	48.2%	**18.71% , 43.34%**
No nausea	50.5%	35.1%	**2.09% , 28.63%**
Total control	48.5%	33.3%	**1.99% , 28.37%**

* Historical control

Reviewer's Comments

The sub-group of 101 patients from Study 402, treated with granisetron 2 mg once daily, and historical control were about comparable with respect to demographic characteristics sex, age and race. However, it was not clear from the submission as to how these two data sets compared with respect to other patient characteristics. None of the confidence intervals in Table 8 included zero indicating supportive evidence in favor of the effectiveness of the granisetron 2 mg once a day dose.

SUPPORTIVE EVIDENCE FROM STUDY 314

Study 314, completed in 1996, was designed to compare the efficacy of a single oral dose of granisetron (2 mg) with the efficacy of a single intravenous dose of ondansetron (32 mg) , given once before chemotherapy, in preventing acute nausea and emesis in patients with malignant disease receiving cisplatin-based chemotherapy at a protocol defined dose of at least 60 mg/m^2. This study was double blind, multicenter, of parallel group design with a total of 1054 patients randomized to the trial, 534 receiving granisetron, and 520 receiving ondansetron, involving a total of 103 U.S. investigational centers. The use of prophylactic dexamethasone or methylprednisone was allowed in the trial.

This study included a sub-group of 117 granisetron-treated (2 mg once daily) patients who did not receive prophylactic corticosteroids. This sub-group is compared to historical controls: 1) granisetron 1 mg bid dose group of Study 022, 2) placebo group of Study 012. The results claimed are as follows:

Table 9
Demographic comparisons:
granisetron 2 mg once day treated sub-group of Study 341 versus historical controls

Demographic Characteristic	Study 341 granisetron 2 mg once daily N=117	*Study 022 granisetron 1 mg bid N=119	* Study 012 placebo group N=14
Gender:			
Female	38 (33%)	71 (60%)	6 (43%)
Male	79 (67%)	48 (40%)	8 (57%)
Mean Age (years)	60.5	54.9	61.1
Race:			
White	93 (79%)	92 (77%)	14 (100%)
Black	16 (14%)	23 (19%)	0
Other	8 (7%)	4 (3%)	0
Mean Body Weight (lbs)	161.5	141.1	142.2
Mean Cisplatin Dose (mg/m^2)	80.9	80.0	80.5

Table 10
Comparative Efficacy results at 24 hours
granisetron 2 mg once a day treated sub-group of Study 341 versus historical controls

Efficacy Endpoints	Study 341 granisetron 2 mg once daily N=117	*Study 022 granisetron 1 mg bid N=111	*Study 012 placebo N=14	95% CI (Abs Diff.) 2 mg once vs. 1 mg bid (Study 022)	95% CI (A. Diff) 2 mg once vs. placebo (Study 012)
Complete Response	52 (44.4%)	41.4%	1 (7.1%)	**-5.1, 20.4%**	**20.9, 53.7%**
No vomiting	68 (58.1%)	48.2%	2 (14.3%)	**-1.8, 23.7%**	**23.2, 64.4%**
No nausea	54 (46.2%)	35.1%	1 (7.1%)	**-9.2, -16.2%**	**22.6, 55.4%**
Total control	47 (40.2%)	33.3%	1 (7.1%)	**-9.1, 16.2%**	**16.7, 49.3%**

* Historical control

Reviewer's Comments

1. Table 10 shows that the lower 95% confidence interval for the difference 'granisetron 2 mg once daily minus granisetron 1 mg bid' with respect to response rates are well within 10%. This supports the case that the effectiveness of the 2 mg dose of granisetron is <u>not</u> inferior to

that of granisetron 1 mg bid dose with a clinically relevant delta of 10%.

2. Also Table 10 supports the case that granisetron 2 mg once daily is effective in comparison to the placebo historical control of Study 012.

OVERALL CONCLUSION

The efficacy data of Study 215 suggest that the 2 mg once a day dose regimen is clinically not inferior to the already approved 1 mg bid dose in the prevention of nausea and vomiting in emetogenic cancer therapy patients studied in this trial. The sponsor's retrospective analysis suggests that the active control in this trial is effective when compared to the historical control prochlorperazine of Study 288. Thus, suggesting that the trial is valid for clinical equivalence efficacy testing.

Additional retrospective historical control analyses, in sub-groups of patients treated with 2 mg once a day dose in Studies 402 and 341, support the above finding.

M. F. Huque, Ph. D.
Mathematical Statistician

Concur: Dr. Smith 4/18/97

cc:
HFD-180/ Archival NDA 20305/ Supplement 001
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-720/Smith
HFD-720/Dr. Huque
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[Huque/reviews\nda\20305sr.y97. April 14, 1997]

STATISTICAL REVIEW & EVALUATION
NDA/Supplement

July 25, 1996

NDA #20-305/Supplement #001
Sponsor: *SmithKline Beecham*
Drug: *(granisetron hydrochloride) Kytril*[R]
Indication: *prevention of nausea and vomiting in emetogenic cancer therapy patients*
Documents Reviewed: Sponsor's submissions April 17, 1995 and June 14, 1996
Medical officer: Dr. Gallo--Torres

This statistical review addresses two clinical trials: Protocols #215 and #436. The sponsor submitted these trials for the claim that the two 1 mg granisetron tablets taken as a single daily dose prior to chemotherapy is an adequate dose regimen alternate to the currently approved dose regimen of 1 mg bid daily indicated for the prevention of nausea and vomiting associated with emetogenic cancer therapy, including high dose cisplatin.

A. PROTOCOL #215

1. Study Design

This was a double-blind, randomized, parallel group study to compare the efficacy and safety of a new dose regimen of granisetron to an approved dose regimen of granisetron in preventing acute nausea and emesis over a 24-hour period in patients receiving moderately emetogenic chemotherapy. The target patient population was adult males and females naive to chemo-therapy, but scheduled to receive moderately emetogenic chemotherapy for malignant disease.

Patients were screened within one week of their scheduled chemotherapy, and were stratified by gender and were randomized to receive either 1 mg oral granisetron bid or 2 mg uid granisetron. To maintain double-blind, each patient received 2 tablets (either 1 active 1 matched placebo, or 2 active depending on the randomized treatment) one hour prior to chemotherapy. A second dose of study medication (either 1 tablet active and 1 placebo, or two tablets placebo) was to be taken by the patient 12 hours after the first dose. Patients were retained at the clinic for at least 1 hour after chemotherapy. They were then dispensed study medication to take it at home for the 12 hour administration. Patients were to record on a "patient-worksheet"diary nausea and emesis information at 6 hour intervals for the 24-hour period following chemotherapy (see attachment #1). Patient inclusion criteria for enrollment were as in attachment #2.

Patients after completing the double-blind portion of the study (cycle #1), were given

options to continue in an open label manner on granisetron 2 mg uid treatment for the subsequent chemotherapy treatment cycles.

The planned primary endpoint was the proportion of patients with complete response defined as having no nausea, no emesis, and no rescue administration during the first 24 hour period (first cycle). Other primary endpoints considered for the first 24-hour period were: the proportion of patients with no emesis, and the proportion of patients with no nausea. The secondary endpoints considered for the first 24-hour period were: frequency of emesis, frequency and maximum severity of nausea, and the incidence of rescue medication.

The trial was planned to establish clinical equivalence to detect a treatment difference of 10 percent in between treatment response rates with 80% power and $\alpha = .05$ with a two-sided alternative hypothesis, on assuming an average response rate of 75 percent. Statistical analyses were planned only for the primary endpoints. The planned analyses were to provided p-values by the Mantel-Haenszel test (M-H test) and the 95% confidence intervals results by the intention-to-treat and per-protocol methods.

2. Sponsor's Analyses and Efficacy Results

A total of 700 patients were randomized, 356 to granisetron 1 mg bid (active control), and 344 to granisetron 2 mg uid. A total of 672 patients completed cycle-1 (randomized DB-period), 341 for active control and 331 for the granisetron 2 mg uid. The remaining 700-672=28 patients discontinued from the trial for various reasons. Attachment #3 (Sponsor Table 3) summarizes patient disposition data. There is a slight imbalance in randomization, otherwise, between-treatment dropout rates appear balanced.

Attachment #4 (Sponsor Table 5) summarizes demographics for all randomized patients. The study included 71-72 percent females, mostly caucasians and mean age groups of Attachment #5 (Sponsor Table 6) gives the frequency of patients by cancer type. The most common primary disease was breast cancer which occurred 49.7 percent in the granisetron 1 mg bid group and 50.1 percent in the granisetron 2 mg uid group. Attachment #6 (Sponsor Table 7) summarizes the most commonly reported chemotherapeutic agents used. The most commonly reported chemotherapeutic agent in female patients was cyclophosphamide (88 percent), with substantial numbers receiving doxorubicin (55 percent) or fluororourcil (51 percent). Males received a variety of agents: cyclophosphamide (39 percent), doxorubicin (39 percent), etoposide (34 percent), cisplatin (31 percent) or vincristine (29 percent). Attachment #7 (Sponsor's Table 9) summarizes the use of rescue medication in the trial. The most frequently rescue medication used was prochloroperazine 11.2 percent in the granisetron 1 mg bid group as compared to 13.1 percent in the granisetron 2 mg uid dose group.

Tables 1 and 2 show the sponsor's primary efficacy results by the intention-to-treat and by the protocol defined methods.

Table 1
Sponsor's Results for the Primary Endpoints, First 24-Hours (Cycle-1)
(Intention-To-Treat Population)

Stratum	Endpoint	granisetron 1 mg bid	granisetron 2 mg uid	Difference % (95% CI)	P-value (M-H test)
female	Complete R.	115/252 (46%)	116/245 (47%)	-1.7 (-10.5, 7.1)	.702
	No emesis	200/252 (79%)	182/245 (74%)	5.1 (-2.3, 12.5)	.180
	No nausea	118/252 (47%)	120/245 (49%)	-2.2 (-10.9, 6.6)	.631
male	Complete R.	64/102 (63%)	57/98 (58%)	4.6 (-9.0, 18.1)	.509
	No emesis	90/102 (88%)	81/98 (83%)	5.6 (-4.2, 15.3)	.264
	No nausea	64/102 (63%)	60/98 (61%)	1.5 (-11.9, 15.0)	.825
combined	**Complete R**	**179/354 (51%)**	**173/343 (50%)**	**0.1 (-7.3, 7.6)**	**.908**
	No emesis	290/354 (82%)	263/343 (77%)	5.2 (-0.8, 11.3)	.088
	No nausea	182/354 (51%)	180/343 (53%)	-1.1 (-8.5, 6.4)	.770

Table 2
Sponsor's Results for the Primary Endpoints, First 24-Hours (Cycle-1)
(Protocol Defined Population)

Stratum	Endpoint	granisetron 1 mg bid	granisetron 2 mg uid	Difference % (95% CI)	P-value (M-H test)
female	Complete R.	101/228 (44%)	103/223 (46%)	-1.9 (-11.1, 7.3)	.687
	No emesis	182/228 (80%)	166/223 (74%)	5.4 (-2.4, 13.1)	.174
	No nausea	104/228 (46%)	107/223 (48%)	-2.4 (-11.6, 6.8)	.615
male	Complete R.	51/86 (59%)	48/83 (58%)	1.5 (-13.4, 16.3)	.847
	No emesis	76/86 (88%)	69/83 (83%)	5.2 (-5.3, 15.8)	.331
	No nausea	51/86 (59%)	50/83 (60%)	-0.9 (-15.7, 13.8)	.901
combined	**Complete R**	**152/314 (48%)**	**151/306 (49%)**	**-0.9 (-8.8, 6.9)**	**.807**
	No emesis	258/314 (82%)	235/306 (77%)	5.4 (-1.0, 11.7)	.098
	No nausea	155/314 (49%)	157/306 (51%)	-1.9 (-9.8, 5.9)	.621

Attachments 8 through 10 includes sponsor's tables which provide descriptive statistics for the secondary efficacy endpoints.

3. Reviewer's Evaluation and Comments/Study 215

Trial Validity

The Study 215 was conducted as a clinical equivalence trial. One of the requirements for a clinical equivalence trial is that the active control in the trial be effective internally within

the same trial. This is usually done by adding a placebo or a low dose group as a third arm in the trial. In the presence of an ethical concern, however, such an effectiveness of the active control is sought by other means, such as, using an appropriate historical placebo control. The sponsor did not address this issue for the Study #215. At least, the sponsor needs to compare the patient population studied in this trial to the patient population used in approving the 1 mg bid dose. The patients studied in this particular trial may not be adequately emetogenic if the delivery rate per time unit of the emetegenic chemotherapeutic agents administered happened to be low; higher this rate more the patients are likely to be emetogenic.

This reviewer is concerned about this issue when given the fact that the second study Protocol #436 gave success rates of only 27% in *males* for the new granisetron regimen based on the 'complete response' endpoint. The corresponding success rate for the 'total control' endpoint was only 18% (see Reviewer Tables 7 and 8, page 9). The medical officer may address this issue on clinical and biological grounds.

Results for Complete Response

On assuming that the trial is valid for clinical equivalence testing, the sponsor's result for the complete response is convincing in favor of clinical equivalence between the two dose regimens. The 90% confidence interval is well within the ± 10% limits for the whole trial, and also for females (see Table 3). However, for males, the 90% confidence interval exceeded ± 10% limits. The sponsor applied the 95% confidence interval criteria for rejecting the test-hypothesis of non-equivalence, but in this reviewer's assessment, 90% confidence interval for clinical equivalence is sufficient for controlling a risk level of 5%, and the per-protocol analysis is more appropriate for this test.

Table 3 (Reviewer Table)
Ninety-Percent (90%) Confidence Interval for the Complete Response Primary Endpoint, 24-Hour (Protocol Defined Population)

Stratum	Response Rate granisetron 1 mg bid	Response Rate granisetron 2 mg uid	Difference (2 gm uid - 1 gm bid) and 90% CI
Females	101/228 (44.3%)	103/223 (46.2%)	1.9%, (-5.8, 9.6)
Males	51/86 (59.3%)	48/83 (57.8%)	-1.5%, (-13.9, 11.0)
Combined	152/314 (48.4%)	151/306 (49.4%)	0.94%, (-5.7, 7.5)

This reviewer did not find any evidence of center-by-treatment interaction in the data for the complete response to invalidate the above results; the Breslow-Day tests gave non-significant p-values.

The following Table 4 shows complete response rate for the granisetron 2 mg uid dose

regimen during repeat cycles of chemotherapy (Cycles 2 through 10). These response rates are for the open label extension of the study, and are numerically greater in magnitude particularly for cycles 5 to 10. It is difficult to rely on the complete response rate estimates for these repeat cycles unless the population at hand is comparable to patients in cycle 1 with respect to emetogenic potential and other key background factors. It was not clear to this reviewer as to why the complete response rate for repeat cycles would systematically go up in comparison to that for cycle 1. This may be due to the fact that repeat cycle patients are not comparable to patients in cycle 1 with respect to emetogenic potential or with respect to relevant demographic and baseline structure. These issues have not been addressed by the sponsor for the repeat cycle claimed results to be interpretable.

Table 4 (Sponsor Table)
Complete Response Rates Over 24-Hours for Repeat Chemotherapy Cycles

Cycle	2 (n=405) N (%)	3 (n=331) N (%)	4 (n=254) N (%)	5 (n=149) N (%)	6 (n=109) N (%)
Male	79 (73.1%)	58 (65.2%)	40 (64.5%)	21 (58.3%)	15 (62.5%)
Female	159 (53.5%)	137 (56.6%)	105 (54.7%)	68 (60.2%)	53 (62.4%)
All	238 (58.8%)	195 (58.9%)	145 (57.1%)	89 (59.7%)	68 (62.4%)

Cycle	7 (n=43) N (%)	8 (n=34) N (%)	9 (n=17) N (%)	10 (n=13) N (%)
Male	12 (85.7%)	6 (66.7%)	4 (80.0%)	3 (75.0%)
Female	22 (75.9%)	17 (68.0%)	8 (66.7%)	7 (77.8%)
All	34 (79.1%)	23 (67.6%)	12 (70.6%)	10 (76.9%)

Data Source: Appendix 7.1.2

Results for Other Primary Endpoints

The 90% confidence intervals results (for females and overall) for the two remaining primary endpoints (the proportion of patients with 'No Emesis', and 'No Nausea, over 24-Hour) were as shown in Table 5. As seen in this table, the two dose regimens are clinically

equivalent with respect to no nausea for the 24-hour period. However, this is not the case for the 'no emesis' endpoint. For this endpoint, 90% confidence limits (-10.7%, -0.04%) was not contained within the ± 10% limits, and did not contain zero, raising the possibility that the granisetron 2 gm uid dose regimen may be slightly inferior to the granisetron 1 mg bid dose in controlling emesis.

Table 4 (Reviewer Table)
Ninety-Percent (90%) Confidence Interval Results for the Proportion of Patients With No Emesis and No Nausea, 24-Hour (Protocol Defined Population)

Stratum	Endpoints	Response Rate granisetron 1 mg bid	Response Rate granisetron 2 mg uid	Difference (2 gm uid - 1 gm bid) and 90% CI
Females	No emesis	182/228 (80%)	166/223 (74%)	-5.4% (-11.9, 1.1)
	No nausea	104/228 (46%)	107/223 (48%)	2.4% (-5.4, 10.1)
Combined	No emesis	258/314 (82%)	235/306 (77%)	-5.4% (-10.7, -0.04)
	No nausea	155/314 (49%)	157/306 (51%)	1.9% (-4.7, 8.5)

B. PROTOCOL 436

This was a single arm open-label, uncontrolled study to evaluate the efficacy and safety of two 1 mg tablets of granisetron hydrochloride given once prior to chemotherapy in the prevention of nausea and vomiting induced by cisplatin-based chemotherapy. The study was a 5-center study with a total of only 30 cancer patients receiving chemotherapy with a cisplatin dose of at least 60 mg/m^2.

At 60 minutes before the start of cisplatin therapy, patients received two 1 mg tablets of granisetron. In cases where more than one chemotherapeutic agent was indicated, cisplatin was the first emetogenic agent given. On a worksheet, patients recorded the date and time of first nausea, the date and time of the first retching or vomiting, the number of emetic episodes over 24 hours, the maximum severity of nausea over 24 hours, and the time of the first administration of rescue medication within the 24 hours, if any. After 24 hours after initiation of cisplatin therapy, the coordinator contacted the patient by telephone, and recorded all information on nausea, vomiting and rescue medication on a source copy of the worksheet. The patients worksheet was not retained. The patient returned to the clinic after approximately 7 days for a follow-up assessment.

The primary efficacy variable was the proportion of patients experiencing total control of symptoms over the 24-hour period following initiation of chemotherapy. This was defined as no vomiting (or retching), no nausea, and no rescue medication. There secondary efficacy endpoints were: 1) no vomiting, defined as no vomiting or retching and no use of rescue

medication; 2) no nausea, defined as no nausea of any severity and no use of rescue medication; 3) complete response, defined as no vomiting or retching, no more than mild nausea, and no rescue medication (this endpoint was retrospectively added).

The sponsor compared the results of this study to the two historical controls: 1) patients who received placebo in the SB Study 012 (historical placebo); patients who received oral granisetrron 1 mg bid in SB Study 022 (positive historical control). Table 5 (Sponsor Table II) presents demographic summary for Study 436 and for the relevant historical controls, and Table 6 (Sponsor Table III) presents sponsor's results.

Table 5
Demographic Summary/ Study 436

Table II. Demographic Characteristics of Study Populations in Study 436 and the Relevant Comparator Groups from Study 012 and Study 022

		Treatment Group		
		Study 436 Two 1 mg Kytril® Tablets Once (N = 30)	Study 012 Placebo IV 5 min. Infusion (N=14)	Study 022 Oral granisetron 1 mg b.i.d. (N=119)
Parameter		n (%)	n (%)	n (%)
Sex	Female	8 (26.7)	6 (42.9)	71 (59.7)
	Male	22 (73.3)	8 (57.1)	48 (40.3)
Race	White	28 (93.3)	14 (100)	92 (77.3)
	Black	1 (3.3)	0	23 (19.3)
	Oriental	1 (3.3)	0	4 (3.4)
Age (years)	Mean	68.5	61.1	54.9
	Range			
Body Wt. (lbs)	Mean	162.0	141.9	143.0
Cisplatin Dose (mg/m^2)	Mean	77.6	80.5	80.0
	Range			

Table 6
Summary of Efficacy Results

Study 436

Parameter	Responders % (95% C.I.)	C.I. of difference^ vs. Study 436
Total Control		
Study 436# (N=30)	30 (11.9, 48.1)	
Study 012## (N=14)	7 (0.2, 33.9)	0.49, 45.23
Study 022@ (N=119)	44 (34.7, 53.0)	-32.70, 5.30
No Vomiting		
Study 436 (N=30)	37 (17.8, 55.6)	
Study 012 (N=14)	7 (0.2, 33.9)	6.49, 52.56
Study 022 (N=119)	56 (47.0, 65.6)	-39.38, 0.11
No Nausea		
Study 436 (N=30)	40 (20.8, 59.2)	
Study 012 (N=14)	7 (0.2, 33.9)	9.60, 56.11
Study 022 (N=119)	45 (35.2, 53.9)	-24.55, 15.47
Complete Response		
Study 436 (N=30)	37 (17.8, 55.6)	
Study 012 (N=14)	7 (0.2, 33.9)	6.49, 52.56
Study 022 (N=119)	52 (42.7, 61.5)	-35.21, 4.34

^ 95% Confidence interval of normal approximation to binomial proportions.
#Study 436, Two 1 mg Kytril® Tablets once; ##Study 012, Placebo IV 5-minute infusion. and @Study 022, oral granisetron 1 mg b.i.d.

Reviewer's Comments/ Study 436

Based on sample size considerations, the trial design is inadequate for establishing clinical equivalence between the new and the approved granisetron dose regimens based positive historical control of oral granisetron 1 mg bid dose derived from the Study 022. The 95 percent confidence intervals for all efficacy endpoints are wide and way beyond the ± 10 percent limits set for establishing clinical equivalence. Therefore, this trial did not provide a statistical evidence of clinical equivalence between the new and the approved dose regimens of granisetron.

The trial indicated effectiveness of the new granisetron dose regimen in comparison to the selected historical placebo. However, the results were driven mainly by the female subgroup (see Reviewer Tables 7 and 8). The response rates in males for the new granisetron regimen were surprisingly low, only 18 percent (2/22) for the 'total control' and 27 percent (6/22) for 'complete response'.

Table 7 (Reviewer Table)
Proportion of Patients with Total Control (Primary Endpoint) and Complete Response By Center and Gender/ Protocol 436 (Treatment = two 1 mg granisetron tablets given once)

Center	Females		Males		Total	
	Total Control	*Complete R*	*Total Control*	*Complete R*	*Total Cont.*	*Complete R*
Center 1	3/4	3/4	0/2	0/2	3/6 (50%)	3/6
Center 2	2/4	2/4	2/5	2/5	4/9 (44%)	4/9
Center 3	0/0	0/0	0/3	0/3	0/3 (0%)	0/3
Center 4	0/0	0/0	1/4	1/4	1/4 (25%)	1/4
Center 5	0/0	0/0	1/8	3/8	1/8) (13%)	3/8 (36%)
Pooled	5/8 (63%)	5/8	4/22 (18%)	6/22 (27%)	9/30 (30%)	11/30 (37%)

Table 8 (Reviewer Table)
Comparison of the Success (Response) Rates for Males (Granisetron 2 mg Once Daily Versus the Historical Placebo Control)

Gender	Endpoint	Granisetron 2 mg Once daily (Protocol 436)	Historical Placebo (Protocol 012)	Difference	2-Sided p# Exact	Asymptotic
Females	Total Control	5/8 (63%)	0/6 (0%)	63%	.031	-
	Complete R	5/8 (63%)	0/6 (0%)	63%	.031	-
Males	Total Control	4/22 (18%)	1/8 (13%)	5%	.808	.691
	Complete R	6/22 (27%)	1/8 (13%)	12%	.502	.327
Combined	Total Control	9/30 (30%)	1/14 (7%)	23%	.1681	.035
	Complete R	11/30 (37%)	1/14 (7%)	30%	.067	.008

For females, by Fisher's Exact. For others, difference in proportions method using StatXact software.

The trial (Protocol 436) seems to exhibit some treatment allocation issues. For example, Center 2 enrolled patients from #9 to #16 in contiguous patient block, but then enrolled patient #20 instead of #17. Patient #17, 18 and 19 were enrolled at Center 3. These treatment allocation inconsistencies may have been due to logistical problems, but was not addressed.

C. OVERALL COMMENTS/CONCLUSION

The first trial (Protocol #215) effectiveness data, on assuming that this trial is valid for clinical equivalence testing, provided statistical evidence to support clinical equivalence between the new claimed and the approved dose regimens of granisertron. For the two primary endpoints, 'complete response' and 'no nausea', the 90% confidence intervals were well within the ± 10% limits for the whole trial, and also separately for females. However, the effectiveness data for 'no emesis', raised the possibility that the new granisetron dose regimen may be slightly inferior to the approved dose; the 90% confidence for this endpoint was not within ± 10% limits and excluded zero.

The second trial (Protocol #436), which was an open label single arm trial with male patients in majority (73%), showed some evidence of effectiveness for the new claimed dose regimen of granisetron in comparison to a selected historical placebo. However, this result was driven mainly by the female subgroup; the observed success rate with respect to the 'total control' of symptoms was 5/8 (63%) for females as compared to only 2/22 (18%) for males.

In the second trial (Protocol #436), the effectiveness difference confidence intervals, for comparing the new granisetron dose regimen with historical positive control of the granisetron bid dose regimen, were quite wide and inconclusive for supporting the hypothesis of clinical equivalence between the new and approved granisetron dose regimen.

M. F. Huque, Ph. D.
Mathematical Statistician

Concur: Dr. Smith 7/31/96

cc:
HFD-180/ Archival NDA 20305/ Supplement 001
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-720/Smith
HFD-720/Dr. Huque
HDF-720/Dr. Al-Osh
HFD-720/File Copy
HFD-720/Chron.
[Huque/reviews\nda\20305s.y96, July 25, 1996]

Attachment #1

Project	Protocol	Center	Patient Number		Page
BRL 43694A	215	0			F

PATIENT WORKSHEET

► Subjective Assessment of Nausea and Emesis

For each scheduled time of assessment:

- record the date and actual time of the assessment
- check one box under Nausea to indicate the severity of nausea for that time interval (e.g., 0-6 hours). If nausea was not experienced, mark none. If asleep for that interval, mark only 'Asleep Entire Interval'. Do NOT mark 'None' also.
- record the number of episodes of emesis (vomiting or retching) during the time interval. If no emetic episodes occurred, record "0".

Scheduled Time of Assessment after Chemotherapy	Date of Assessment (day month year)	Time (24 hr. clock)	Nausea					Episodes of Emesis
			Asleep Entire Interval	None	Mild	Moderate	Severe	
Hours (0-6 hours)			☐	☐	☐	☐	☐	
12 Hours (6-12 hours)			☐	☐	☐	☐	☐	
18 Hours (12-18 hours)			☐	☐	☐	☐	☐	
24 Hours (18-24 hours)			☐	☐	☐	☐	☐	

► Study Medication

Study medication is to be taken 12 hours after the start of chemotherapy. Record the date and time study medication was taken.

Date (day month year)	Time (24 hr. clock)	Were both tablets taken?	
		Yes	No
		☐	☐

► Time of First Medication For Nausea or Emesis

Did you take any medication for nausea or emesis during the 24 hour period following chemotherapy?

☐ Yes ☞ Record medication, date and time

☐ No

Name of Medication	Date (day month year)	Time (24 hr. clock)

► Other Medications or Comments

Record any other medication OR any complaints you experience during the 24 hour period following chemotherapy on the back of the worksheet.

Following completion of cycle 1 of chemotherapy, patients were given the opportunity to receive open-label granisetron, 2 mg uid, on the first day of each subsequent cycle of chemotherapy.

CRITERIA FOR INCLUSION: Patients who meet the following criteria were eligible to participate in the study:

(1) adult (≥18 years) male and female cancer patients, naive to emetogenic chemotherapy;

(2) scheduled to receive one of the following chemotherapeutic agents, either as a single agent or in combination:

• cisplatin	≥20mg m^2 to ≤50 mg/m^2
• oral cyclophosphamide	≥100 mg/m^2
• iv cyclophosphamide	≥500 mg/m^2
• carboplatin	≥300 mg/m^2
• dacarbazine	≥300 mg/m^2
• doxorubicin	>40 mg/m^2 (single agent)
	≥25 mg/m^2 (in combination)

(3) Karnofsky performance status score of at least 60% or an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less;

(4) acceptable vital signs, hematology and clinical chemistry results;

(5) receiving no concurrent medications with significant antiemetic activity;

(6) no nausea and/or vomiting within the 24-hour period prior to the administration of study medication;

(7) signed informed consent and willing and able to comply with the protocol directives.

TABLE 3: PATIENT DISPOSITION FOR CYCLE 1 - NUMBER AND PERCENT OF PATIENTS WITHDRAWN

Patient Status	Granisetron 1 mg bid N (%)	Granisetron 2 mg uid N (%)	Total N (%)
Completed Cycle I	341 (95.8)	331 (96.2)	672 (96.0)
Reasons for Discontinuation			
Adverse Experience, Including Intercurrent Illness	2 (0.6)	1 (0.3)	3 (0.4)
Lack of Efficacy	2 (0.6)	4 (1.2)	6 (0.9)
Protocol Violation Including Non-Compliance	10 (2.8)	7 (2.0)	17 (2.4)
Other Reason(s)	1 (0.3)	1 (0.3)	2 (0.3)
TOTAL	356 (100%)	344 (100%)	700 (100%)

Data Source: Appendix 5.2, 5.3, and 8.15

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ON ORIGINAL

TABLE 5: DEMOGRAPHIC CHARACTERISTICS FOR ALL PATIENTS

	Granisetron 1 mg bid (n=356)	Granisetron 2 mg uid (n=344)	p - value
Gender	N (%)	N (%)	
Male	103 (29)	98 (28)	0.897
Female	253 (71)	246 (72)	
Age, (years)			
Mean + SD	55.3 + 13.8	56 + 14.2	0.535
Min, Max			
Race			
Black	43 (12)	41 (12)	0.582
Caucasian	293 (82)	291 (85)	
Oriental	4 (1)	3 (0.87)	
Other	16 (4.49)	9 (2.62)	
Weekly Alcohol Consumption*	(n=355)	(n=341)	
Mean	3.6	4.7	0.403
STD	10.5	23.7	
Min			
Max			

1 unit = 150 ml of wine, or 0.25 L of beer, or 50 ml of spirits (Average weekly consumption)
Data Source: Appendix 2.1 and 2.3

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TABLE 6: DISTRIBUTION OF PATIENTS BY PRIMARY DISEASE SITE

Primary Disease Site	Granisetron 1 mg bid	Granisetron 2 mg uid	Total
Patients (%) Enrolled	**N (%)**	**N (%)**	**N (%)**
Breast	177 (49.7)	172 (50.1)	349 (49.9)
Lymphoma	56 (15.7)	47 (13.7)	103 (14.7)
Lung	43 (12.1)	49 (14.3)	92 (13.2)
Other	34 (9.6)	38 (11.1)	72 (10.3)
Ovary	25 (7.0)	22 (6.4)	47 (6.7)
Testis	9 (2.5)	5 (1.5)	14 (2.0)
Head / Neck	5 (1.4)	6 (1.7)	11 (1.6)
Soft Tissue Sarcoma	6 (1.7)	3 (0.9)	9 (1.3)
Cervix	1 (0.3)	1 (0.3)	2 (0.3)
Total	**356**	**343**	**699**

Data source: Appendix 3.1

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TABLE 7: MOST FREQUENTLY REPORTED CHEMOTHERAPEUTIC REGIMEN BY TREATMENT GROUP AND GENERIC TERM - CYCLE I

Chemotherapeutic Agent	Granisetron 1 mg bid (N=356) N (%)	Granisetron 2 mg uid (N=344) N (%)	Total (N=700) N (%)
Male Patients	103 (100)*	98 (100)	201 (100)
Cyclophosphamide	37 (35.9)	42 (42.9)	79 (39.3)
Doxorubicin	32 (31.1)	47 (48.0)	79 (39.3)
Carboplatin	25 (24.3)	15 (15.3)	40 (19.9)
Etoposide	34 (33.0)	34 (34.7)	68 (33.8)
Vincristine	25 (24.3)	34 (34.7)	59 (29.4)
Cisplatin	32 (31.1)	31 (31.6)	63 (31.3)
Prednisone	22 (21.4)	21 (21.4)	43 (21.4)
Female Patients	253 (100)*	246 (100)*	499 (100)
Cyclophosphamide	221 (87.4)	216 (87.8)	437 (87.6)
Doxorubicin	142 (56.1)	132 (53.7)	274 (54.9)
Fluorouracil	127 (50.2)	127 (51.6)	254 (50.9)
Carboplatin	37 (14.6)	37 (15.0)	74 (14.8)
Methotrexate	56 (22.1)	56 (22.8)	112 (22.4)
All Patients	356 (100)	344 (100)	700 (100)
Cyclophosphamide	258 (72.5)	258 (75.0)	516 (73.7)
Doxorubicin	174 (48.9)	179 (52.0)	353 (50.4)
Fluorouracil	137 (38.5)	134 (39.0)	271 (38.7)
Carboplatin	62 (17.4)	52 (15.1)	114 (16.3)
Methotrexate	58 (15.8)	58 (16.9)	116 (16.6)
Etoposide	47 (13.2)	46 (13.4)	93 (13.3)
Vincristine	40 (11.2)	52 (15.1)	92 (13.1)
Cisplatin	40 (11.2)	44 (12.8)	84 (12.0)

* One patient did not receive chemotherapy

Data Source: Appendix 4.3

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TABLE 9: MOST FREQUENTLY REPORTED ANTIEMETIC RESCUE MEDICATION FOR CYCLE 1

Antiemetic Rescue Medication	Granisetron 1 mg bid (N=356) N (%)	Granisetron 2 mg uid (N=344) N (%)	Total (N=700) N (%)
Prochlorperazine	40 (11.2)	45 (13.1)	85 (12.1)
Lorazepam	9 (2.5)	7 (2.0)	16 (2.3)
Thiethylperazine Maleate	5 (1.4)	10 (2.9)	15 (2.1)
Promethazine Hydrochloride	7 (2.0)	3 (0.9)	10 (1.4)

Data Source: Appendix 4.4

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TABLE 19: FREQUENCY OF EMETIC EPISODES OVER 24-HOURS - CYCLE 1 (INTENT-TO-TREAT POPULATION)

Stratum	Statistic	Granisetron 1 mg bid	Granisetron 2 mg uid
Female	N (Missing)	250 (3)	244 (2)
	Mean (SD)	0.85 (2.56)	0.94 (2.61)
	Range		
Male	N (Missing)	102 (1)	98 (0)
	Mean (SD)	0.30 (1.23)	0.37 (1.16)
	Range		
Combined	N (Missing)	352 (4)	342 (2)
	Mean (SD)	0.69 (2.27)	0.78 (2.31)
	Range		

Data Source: Appendix 7.5

TABLE 20: INCIDENCE AND MAXIMUM SEVERITY OF NAUSEA OVER 24-HOURS - CYCLE 1 (INTENT-TO-TREAT POPULATION)

Stratum	Nausea Severity	Granisetron 1 mg bid N (%)	Granisetron 2 mg uid N (%)
Female	Unknown	1 (0.4)	1 (0.4)
	None	118 (46.8)	120 (49.0)
	Mild	71 (28.1)	57 (23.2)
	Moderate	31 (12.3)	33 (13.4)
	Severe	31 (12.3)	33 (13.4)
	Present [a]	1 (0.4)	1 (0.4)
Male	Unknown	1 (1.0)	0
	None	64 (62.7)	60 (61.2)
	Mild	28 (27.2)	20 (20.4)
	Moderate	7 (6.8)	12 (12.2)
	Severe	3 (2.9)	6 (6.1)
Combined	Unknown	2 (0.6)	1 (0.3)
	None	182 (51.4)	180 (52.5)
	Mild	99 (27.8)	77 (22.4)
	Moderate	38 (10.7)	46 (13.4)
	Severe	34 (9.6)	39 (11.3)
	Present [a]	1 (0.3)	1 (0.3)

[a] - Nausea present but severity is unknown.

Data Source: Appendix 7.6

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TABLE 21: FREQUENCY OF ANTIEMETIC RESCUE MEDICATION OVER 24-HOURS (INTENT-TO-TREAT POPULATION)

Stratum	Statistic	Granisetron 1 mg bid	Granisetron 2 mg uid
Female	N (Missing)	252 (1)	245 (1)
	Mean (sd)	0.62 (1.47)	0.60 (1.32)
	Range		
Male	N (Missing)	102 (1)	98 (0)
	Mean (sd)	0.26 (0.77)	0.43 (1.22)
	Range		
Combined	N (Missing)	354 (2)	343 (1)
	Mean (sd)	0.52 (1.31)	0.55 (1.29)
	Range		

Data Source: Appendix 7.7

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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020305 (S001)

ADMINISTRATIVE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-305/S-001

Name of Drug: Kytril (granisetron) Tablets

DEC 12 1997

Sponsor: SmithKline Beecham Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): 10/20/97

Receipt Date(s): 10/21/97

Background and Summary Description:
See the October 3, 1997 labeling review for a complete history of this supplemental application. The application was submitted to provide for a single 2 mg dose as an alternative to the 1 mg dose given twice daily, and was approved October 6, 1997 based on draft labeling submitted September 5, 1997. The firm has now submitted final printed labeling.

Review

The submitted labeling (KY:L3T, DATE OF ISSUANCE OCT. 1997) was compared to that submitted on September 5, 1997, and they are identical.

Conclusions

An Acknowledge and Retain letter should be drafted.

Kate Johnson 12/12/97
Consumer Safety Officer

A Tolen 12-12-97

cc:
Original NDA 20-305/S-001
HFD-180/Div. Files
HFD-180/KJ

draft: kj/December 12, 1997/c:\wpfiles\cso\n\20305rkj.s01
CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

Johnson

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-305/S-001

OCT - 3 1997

Name of Drug: Kytril (granisetron) Tablets

Sponsor: SmithKline Beecham

Material Reviewed

Submission Date(s): September 5, 1997

Receipt Date(s): September 8, 1997

Background and Summary Description:
This supplement was originally submitted April 17, 1995 to provide for a single 2 mg QD dose as an alternate to the approved 1 mg BID for the prevention of nausea and vomiting due to cancer chemotherapy, including high dose cisplatin.

The application was resubmitted on September 19, 1995, and contained reports for Studies 215, which compared the 2 mg QD dose to the 1 mg BID dose, and 436, which compared the proposed 2 mg dose with a historical control of the 1 mg twice daily dosing regimen. The application was not approved on October 16, 1996 because, although in Study 215, the doses appeared equivalent, no data was provided to demonstrate that either arm was active. In addition, the results for complete response were lower than expected (it was later determined that the results were for total response, not complete response). Finally, in Study 436, the effectiveness confidence intervals for comparing the 2 mg QD dose with historical positive control of twice daily dose regimen were wide and did not support the hypothesis of clinical equivalence between the proposed and approved dose regimen.

The firm responded to the not approvable letter on February 21, 1997. To validate the efficacy of the active treatments in Study 215, the submission contained a comparison of the results for Study 215 for the Kytril treatments to the prochlorperazine group from Study 288 (historical control). The submission also contained results from Studies 402 and 341 which further substantiated the efficacy of the 2 mg QD dosing regiment. In these studies, Kytril 2 mg was compared to the currently approved 32 mg ondansetron IV dose in patient receiving moderately and highly emetogenic chemotherapy, respectively. Dexamethasone use was allowed in both of these studies. In Study 402, results from the subset of patients receiving 2 mg QD (without dexamethasone) were compared to the PCPZ historical control in Study 288. In Study 341, data from those patients receiving 2 mg QD (without

dexamethasone) were compared to the 1 mg BID group from Study 022 (historical positive control group) and to placebo from Study 012. These evaluations showed that the 2 mg QD was statistically superior to placebo, and provided similar efficacy to the 1 mg BID dose comparator for complete response.

The application was AE on August 21, 1997, pending final printed labeling.

Review

The firm has submitted revised draft labeling that incorporates the revisions requested in the AE letter. The firm is also requesting some additional revisions to the clinical trials section of the package insert. These changes and the firm's rationale for the changes are located in Attachment I. The reviewing medical officer, Dr. Hugo Gallo-Torres found these modifications acceptable.

Conclusions

An AP letter should be drafted.

Kati Johnson 10/3/97

Consumer Safety Officer

APPEARS THIS WAY
ON ORIGINAL

Attachment

cc:
Original
HFD-180/Div. Files
HFD-180/KJohnson
draft: kj/October 3, 1997/c:\wpfiles\cso\n\20305710.r2

Gallo-Torres MD 10-3-97

CSO REVIEW

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ATTACHMENT 1

Changes to FDA Approved Draft Labeling

Revision 1: Change to the table designated as Table 3 (page 000121 of FDA draft labeling).

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

	Percentages of Patients		
Efficacy Measures	*Oral Kytril 1 mg b.i.d (n=354) %*	*Oral Kytril 2 mg q.d. (n=343) %*	*Prochlorperazine[2] 10.0 mg b.i.d (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*

Rationale for Revision

- We added the efficacy parameter "complete response" for greater consistency with the other effectiveness tables in this labeling as well as in the Kytril IV prescribing information.

- Support for this revision was provided in the February 20, 1997 submission cited in the approvable letter, Volume 2, beginning on page 000149. A copy of the relevant pages is provided as Attachment 3.

Revision 2. Statement regarding the third double-blind trial (Page 000122 of FDA draft labeling).

The FDA recommended statement is as follows:

"Results from a Kytril 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. At 24 hours, Kytril 2 mg QD was statistically superior to PCPZ for complete response (defined as no vomiting and more than mild nausea)."

SB has chosen to expand the statement to read as follows:

"Results from a Kytril 2 mg q.d. alone treatment arm in a third double-blind, randomized trial, were compared to prochlorperazine (PCPZ), 10 mg b.i.d., derived from a historical control. The 24 hours results for Kytril 2 mg q.d. 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."

Rationale for Revision

- We appreciate the Division's move to simplify labeling. However, we believe that the single statement of the efficacy results, for this study, does not provide enough information for the physician to make a decision to use the 2 mg once regimen in patients receiving moderately emetogenic chemotherapy. We believe that the expanded statement, which gives the physician information on key elements of the emetogenic response (complete response, vomiting, nausea, and total control), accomplishes this goal.

- Support for this revision was provided in the February 20, 1997 submission cited in the approvable letter, Volume 77, beginning on page 000018. The relevant pages are included as Attachment 4.

Revision 3. Statement regarding the third double-blind trial (Page 000123 of FDA draft labeling).

The FDA recommended statement is as follows:

"Results from a Kytril 2 mg QD alone treatment arm in a second double-blind, randomized trial were compared to both Kytril 1 mg BID and placebo historical controls. At 24 hours, Kytril 2 mg QD was statistically superior to placebo, and was comparable to Kytril 1 mg BID for complete response (defined as no vomiting and no more than mild nausea)."

SB has chosen to expand the statement to read as follows:

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

Rationale for Revision

- As noted in the previous rationale statement, the expanded description of the results, with key elements of the emetogenic response and rates of improvement, will provide the physician with the important information needed to make a decision to use the 2 mg once regimen.

- Support for this revision is in the February 20, 1997 submission cited in the approvable letter, Volume 118, beginning on page 000085. The relevant pages are included as Attachment 5.

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-305/S-001

AUG 20 1997

Name of Drug: Kytril (granisetron hydrochloride) Tablets

Sponsor: SmithKline Beecham Pharmaceuticals

Material Reviewed

Submission Date(s): February 20, 1997

Receipt Date(s): February 21, 1997

Background and Summary Description:

This supplement was originally submitted April 17, 1995 to provide for a single 2 mg QD dose as an alternate to the approved 1 mg BID for the prevention of nausea and vomiting due to cancer chemotherapy, including high dose cisplatin.

The application was resubmitted on September 19, 1995, and contained reports for Studies 215, which compared the 2 mg QD dose to the 1 mg BID dose, and 436, which compared the proposed 2 mg dose with a historical control of the 1 mg twice daily dosing regimen. The application was not approved on October 16, 1996 because, although in Study 215, the doses appeared equivalent, no data was provided to demonstrate that either arm was active. In addition, the results for complete response were lower than expected (it was later determined that the results were for total response, not complete response). Finally, in Study 436, the effectiveness confidence intervals for comparing the 2 mg QD dose with historical positive control of twice daily dose regimen were wide and did not support the hypothesis of clinical equivalence between the proposed and approved dose regimen.

The firm responded to the not approvable letter on February 21, 1997. To validate the efficacy of the active treatments in Study 215, the submission contained a comparison of the results for Study 215 for the Kytril treatments to the prochlorperazine group from Study 288 (historical control). The submission also contained results from Studies 402 and 341 which further substantiated the efficacy of the 2 mg QD dosing regiment. In these studies, Kytril 2 mg was compared to the currently approved 32 mg ondansetron IV dose in patient receiving moderately and highly emetogenic chemotherapy, respectively. Dexamethasone use was allowed in both of these studies. In Study 402, results from the subset of patients receiving 2 mg QD (without dexamethasone) were compared to the PCPZ historical control in

Study 288. In Study 341, data from those patients receiving 2 mg QD (without dexamethasone) were compared to the 1 mg BID group from Study 022 (historical positive control group) and to placebo from Study 012. These evaluations showed that the 2 mg QD was statistically superior to placebo, and provided similar efficacy to the 1 mg BID dose comparator for complete response.

Review

The proposed labeling was compared to the currently approved package insert (KY:L1T, approved 3/16/95 with the original NDA). No other revisions have been made other than those highlighted by the firm in the annotated labeling submitted with this supplement. A side-by-side comparison of the currently approved labeling and proposed FDA revisions is attached. If there are no FDA revisions cited, then the firm's proposal is acceptable. Comments on the specific revisions, by section, follows:

1. **Pharmacokinetics section**. This portion of the labeling has been revised to include information on pediatrics. This information was submitted and approved for the Injection application (NDA 20-239/S-002, approved January 21, 1997). This is an appropriate revision for the tablet application.

2. **Clinical Trials**.

   The firm has divided the section into Moderately Chemotherapy and Cisplatin-Base Chemotherapy. This is consistent with labeling for the other currently approved $5HT_3$ receptor antagonist, Zofran (ondansetron),
   As a result of this revision, the introductory paragraph to the section has been revised, and introductory sentences for each of the subsections have been added.

   To eliminate repetition, the proposed introductory paragraph for the section has been revised to incorporate the introductory sentences from each of the subsections.

   Moderately Emetogenic Chemotherapy Subsection:

   A. I suggest that one of the previously described trials be deleted.

      When Kytril Tablets were approved on March 16, 1995, the clinical trials section contained information on two studies in patients receiving moderately emetogenic chemotherapy. For the first study, the narrative and accompanying Table describe the efficacy of the 1 mg BID dose. The second study narrative

and accompanying Table describe the superiority of the 1 mg BID dose to an active historical control, prochlorperazine [(PCPZ) 10 mg BID, from Study 288]. The firm would like to retain the original two studies, and then add results from Studies 215 and 402 (see Background above, and "C" below). Since the proposed narrative and Table from Study 215 describe results efficacy of Kytril 1 mg BID and 2 mg QD compared to PCPZ, retention of a description of the second study is redundant.

B. The narrative and description of the third study in moderately emetogenic chemotherapy has been slightly revised. From the proposed narrative, it is not clear that the efficacy of Kytril 1 mg BID and 2 mg QD were retrospectively compared to the PCPZ treatment arm from Study 288 (see "B" above).

C. The narrative description of the fourth study (Study 402) was significantly revised to focus on the information which was used to support approval of the supplement under review. In this study, oral Kytril 2 mg QD was compared to intravenous Zofran (ondansetron), 32 mg, with patients stratified by use or non-use of corticosteroids. Efficacy in the subgroup of patients who received Kytril 2 mg QD WITHOUT steroids was retrospectively compared to the PCPZ treatment arm in Study 288 (see "B" and "C" above). All references to the comparison between Kytril 2 mg and Zofran Injection 32 mg have been deleted. The inclusion of the information on Zofran and corticosteroids (dexamethasone) proposed by the firm may allow them to promote that Kytril 2 mg QD and Zofran 32 mg IV are "comparable" and that use of dexamethasone enhances efficacy in this population. More studies may be needed to substantiate this claim.

Cisplatin-based Chemotherapy

In the currently approved labeling, there is a single study which describes the efficacy of Kytril 1 mg BID in this patient population. The firm proposes to include a narrative almost identical to that proposed under "C" above, albeit for a different (Kytril vs. Zofran) study (Study 341). Similar revisions to those described above, have also been made to this subsection of the proposed package insert.

3. **Adverse Reactions:**

This section has been revised to reflect the addition of patients who participated in Studies 402 and 341. If the comparison to Zofran Injection is not being used as the basis of approval of this supplement, the adverse events of those patients should not be included in this revision. The percentages should be adjusted accordingly

4. **Dosage & Administration**

This section has appropriately been revised to describe both regimens.

Conclusions

An approvable letter, pending final printed labeling identical in content to the attached draft, should be drafted.

Kate Johnson 8/20/97
Consumer Safety Officer

APPEARS THIS WAY
ON ORIGINAL

Carmen Holcombe 8-20-97

cc:
Original
HFD-180/Div. Files
HFD-180/KJohnson

draft: kj/August 8, 1997/c:\wpfiles\cso\n\20305s01.r2
r/d Initials:HGAllo-Torres 8/18/97
08/20/97 NDeed. H G-T

APPEARS THIS WAY
ON ORIGINAL

CSO REVIEW

EXCLUSIVITY SUMMARY for NDA # 20-305 SUPPL # 001

Trade Name Kytril Tabs **Generic Name** granisetron
Applicant Name SmithKline Beecham **HFD-** 180

Approval Date 10/6/97

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 / / NO / X /

   b) Is it an effectiveness supplement?

   YES / X / NO / /

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

   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 / X / NO / /

   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:

_____

_____

APPEARS THIS WAY
ON ORIGINAL

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?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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?

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

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 /X/ NO /___/

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

NDA # 20-239 Kytril Injection

NDA # 20-305 Kytril Tablets

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

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 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /_x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 /_x_/ 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 8:**

_____

_____

(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 /_X_/

(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 # 215**

Investigation #2, Study # _____

Investigation #3, Study # _____

**This study was found acceptable only after the firm referenced an historical control from Study 288, which was used to approve the initial NDA.

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 /_x_/
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 /_x_/
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 # 215

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 /_x_/ 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 /x /

If yes, explain: ________________________________

Kate Johnson 12/22/97
Signature Date
Title: Supervisory Consumer Safety Officer

APPEARS THIS WAY
ON ORIGINAL

12-22-97
Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-~~85~~ 93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20305 Supplement # S-001 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Kytril (granisetron) Tablets Action: AP AE NA

Applicant SmithKline Beecham Therapeutic Class 3 S

Indication(s) previously approved prevention of chemotherapy induced nausea & vomiting
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Indication in this application N/A (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

✓ 5. **If none of the above apply,** attach an explanation, as necessary.

Supplement provides for BID instead of QD dosing.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Kathi Johnson
Signature of Preparer and Title

10/3/97
Date

cc: Orig NDA/PLA/PMA #_____
HF_____/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020305 (S001)

CORRESPONDENCE

NDA 20-305/S-001

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

OCT 16 1996

Dear Dr. Pinkett:

Please refer to your April 17, 1995 supplemental new drug application and your resubmission dated October 19, 1995 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron HCl) Tablets.

We acknowledge receipt of your amendments dated June 14, August 22, and September 4, 1996.

This supplemental application provides for a single 2 mg dose as an alternative to the 1 mg dose given twice daily.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

In Study 215, the 2 mg daily dose appears to be equivalent to the 1 mg twice daily dose for complete response and for no nausea, but no data has been provided to demonstrate that either arm was active. The results for both 2 mg daily and 1 mg twice daily doses were compared to two relevant historical controls; granisetron 0.25 mg twice daily (from Study 021), and prochlorperazine 10 mg twice daily (from Study 288). We could not demonstrate that the dose regimens were effective in this study. In addition, the results for complete response were lower than expected, and might represent total response rates rather than complete response rates.

In the second trial (Study 436), the effectiveness difference confidence intervals, for comparing the new granisetron dose regimen with historical positive control of the granisetron twice daily dose regimen, were quite wide and inconclusive for supporting the hypothesis of clinical equivalence between the new and approved granisetron dose regimen.

You may wish to review the calculations for complete response in Study 215, and provide analyses compared to an appropriate historical control to demonstrate that the dose regimens were effective in this study.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental application. Any amendments 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.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

kj 10/16/96
sf 6-T 10/16/96

cc:
Original NDA 20-305/S-001
HFD-180/Div. files
HFA-100
HFD-2/M.Lumpkin
HFD-103/P.Botstein
HFD-101/L.Carter
DISTRICT OFFICE
HFD-80
HFD-180/K.Johnson
HFD-180/HGallo-Torres

sf 10/16/96

APPEARS THIS WAY
ON ORIGINAL

drafted: kj/October 15, 1996/c:\wpfiles\cso\n\20305610.s01
r/d Initials: Sfredd 10/16/96
final:10/16/96

NOT APPROVABLE (NA)

NDA 20-305/S-001

DEC 15 1997

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

Dear Dr. Pinkett:

We acknowledge the receipt of your October 20, 1997 submission containing final printed labeling in response to our October 6, 1997 letter approving your supplemental new drug application for Kytril (granisetron hydrochloride) Tablets.

We have reviewed the labeling that you have submitted in accordance with our October 6, 1997 letter, and we find it acceptable.

Sincerely yours,

LT 12-12-97

12/12/97

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-305
HFD-180/Div. Files
HF-2/Medwatch (with labeling)
HFD-103/Office Director (with labeling)
HFD-180/CSO/K.Johnson
HFD-40/DDMAC (with labeling)
HFD-92/DDM=DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

APPEARS THIS WAY
ON ORIGINAL

Drafted by: kj/December 12, 1997/c:\wpfiles\cso\n\20305712.s01

ACKNOWLEDGE AND RETAIN (AR)

26.1

NDA 20-305/S-001

AUG 29 1997

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

Dear Dr. Pinkett:

Please refer to your supplemental new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron hydrochloride) Tablets.

Per your request of August 25, 1997, we are enclosing a copy of the June 3, 1997 medical review for this application.

We hope this information is helpful.

If you have any questions, please contact Kati Johnson, Supervisory Consumer Safety Officer, at (301) 443-0487.

APPEARS THIS WAY
ON ORIGINAL

KJ 8/26/97

Sincerely yours,

CT 8-26-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-305/S-001
HFD-180/Div. Files
HFD-180/CSO/K.Johnson

APPEARS THIS WAY
ON ORIGINAL

Drafted by: kj/August 26, 1997/c:\wpfiles\cso\n\20305s01.708

GC

NDA 20-305/S-001

SmithKline Beecham Pharmaceuticals
Attention: Olivia Pinkett, Ph.D.
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

MAR 6 1997

Dear Dr. Pinkett:

We acknowledge receipt on February 21, 1997 of your February 20, 1997 amendment to your supplemental new drug application (NDA) for Kytril (granisetron) Tablets.

This amendment contains additional clinical information submitted in response to our October 16, 1996 not approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is August 21, 1997.

If you have any questions, please contact Kati Johnson, Supervisory Consumer Safety Officer, at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-305/S-001
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: kj/February 28, 1997/c:\wpfiles\cso\n\20305702.0kj
ACKNOWLEDGEMENT (AC)

NDA 20-305/S-001

SmithKline Beecham Pharmaceuticals
Attention: Olivia Pinkett, PhD
4 Falls Corporate Center
Rt. 23 & Woodmont Ave., P.O. Box 1510
King of Prussia, PA 19406

OCT 27 1995

Dear Dr. Pinkett:

We acknowledge receipt of your resubmitted supplemental application. Although originally submitted as Supplement -002, in our October 24, 1995 telephone conversation it was determined that the submission was a resubmission of Supplement -001 which was refused for filing on June 13, 1995. Please note the following information:

Name of Drug Product: Kytril (granisetron hydrochloride) Tablets

NDA Number: NDA 20-305

Supplement Number: S-001

Therapeutic Classification: Standard

Date of Resubmitted Supplement: October 19, 1995

Date of Receipt: October 20, 1995

This supplement provides for a single 2 mg dose as an alternative to the 1 mg dose given twice daily.

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 December 19, 1995 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

kj 10/25/95

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

cc:
Original NDA 20-305/S-001
HFD-180/Div. Files
HFD-80
HFD-180/CSO/K.Johnson

drafted: kj/October 25, 1995/c:\wpfiles\cso\n\20305510.0kj

SUPPLEMENT ACKNOWLEDGEMENT

c. Comparability of Groups/Patient Baseline Characteristics

As shown in Table 2, the two groups were comparable to each other in demographic characteristics, primary disease site, Karnofsky status, ECOG scale and chemotherapy agents. In this trial, 71.5% of the patients were female, while 28.5 were male, the mean age was 55.5 years

Half of the patients had breast cancer, 15% had lymphoma, 13% had cancer of the lung; 6.5% had cancer of the ovaries. Cancer of the testis, soft tissue sarcoma, head/neck and cervix occurred in 3% or less of the patients; location for other cancers was 36% for the rest of the patients. The most commonly used primary chemotherapeutic agent was cyclophosphamide (74% of the patients), followed by doxorubicin (50.5%), 5-FU (38%) and MTX (16.5% of the patients). As per platinum-based regimens, carboplatin was given to 16% of the patients and cisplatin to 12% of the patients. The emetogenic potential of the chemotherapeutic agents are best characterized as being mainly non-cisplatin and of moderate emetogenic potential.

d. Cycles 2 through 10: Recorded Reasons for Patient Withdrawal/Number of Patients Evaluated for Efficacy (Table 3)

This Table lists the number of patients participating in chemotherapy cycle 2 through 10 (the number of patients per Cycle 11 through 16 was 7 or less per cycle). In Table 3, a steady decrease in the number of patients completing Cycle 2 through 10 is documented (Cycle 2, n=406, Cycle 10, n=11).