Table 27

Most Frequent Adverse Events by preferred term during TBI Percentage of Patients

Adverse Event	Treatment Group	
	Granisetron(n=16) (n)(%)	Comparator Combination(n=14)(n)(%)
Fever	(3)(18.8%)	(3)(21.4%)
Hypertension	(2)(12.5%)	(2)(14.3%)
Diarrhea	(2)(12.5%)	(2)(14.3%)
Dysphagia	(2)12.5%)	0
Sialadenitis	(5)(31.3%)	(5)(35.7%)
Stomatitis	(1)(6.3%)	(3)(21.4%)
Arthralgia	(1)(6.3%)	(2)(14.3%)
Back Pain	(1)(6.3%)	(2)(14.3%)
Infection	(1)(6.3%)	(4)(28.6%)
Esophagitis	0	(2)(14.3%)

(Table modified from sponsor's table 13, Vol 10, p.56)

The small number of patients represented in Table 27 (i.e., a total of 30) makes the cited percentages useful only in a relative sense.

Reviewer's Comment: The sole outlier as a comparatively more frequently-occurring adverse event during TBI in this study was Sialadenitis (i.e., salivary gland inflammation), which was reported as an adverse event with equal frequency in both treatment groups. This adverse event was not reported at all in the most comparable study in the present submission. #448. Neither was it reported in pivotal study #259. Even though the numbers are small, the reviewer is puzzled at this phenomenon. The seriousness of the related symptomatology and even a definition of the symptoms is not made clear by the sponsor. Possibly, its occurrence at all is related to the intensity with which radiation was delivered in this particular study, i.e., less than a single day, which makes it different from the others. Since this is pure speculation, no further comment can be added. As this more intense mode of delivering radiotherapy is no longer in practice, it is possible that this explains why this particular adverse event has not been further seen.

During conditioning chemotherapy, 38.1% of patients in the granisetron and 50% of the patients in the conditioning chemotherapy groups, reported at least one adverse event of which only five occurred in as many as 10% of patients. These symptomatic events again involved small numbers of patients and were only five in number affecting less than 20% of patients in either treatment group. The events were as follows: allergic reaction, fever, headache, anxiety, and somnolence. There was no obvious difference in pattern between the treatment groups.

Serious Adverse Events

During the TBI phase, 3 of 16 patients in the granisetron and 3 in the comparator combination group, reported a serious adverse event. The three serious adverse events for granisetron were: 1) intense shoulder pain during the TBI period; 2) fever and anorexia; and 3) parotiditis/sialadenitis. For the comparator group, the three serious adverse events were: 1) Multi-organ failure with pneumonia, septicemia, with impairment of both liver and renal function; 2) stomatitis and "mucitis"; and 3) chills and fever during TBI.

Deaths

One patient who had received granisetron during the conditioning chemotherapy phase and then had been re-randomized to receive a comparator antiemetic combination during TBI died 28 days after last receiving study medication. He developed circulatory failure and shock and died due to multi-organ failure. The investigator considered that the death was unrelated to the study medication.

Withdrawals Due to Adverse Experiences

During the TBI phase of the study, two patients were withdrawn from the granisetron treatment group. One patient suffered from shoulder pain/arthralgia after 6 hours of TBI for which therapy was given and the event resolved. A second patient was suffering from severe anxiety that had started during treatment with comparator antiemetic combination in the conditioning chemotherapy phase of the study; however, the withdrawal occurred during TBI after the patient had received treatment during this phase of the study. During conditioning chemotherapy, there were two patients who suffered significant AEs leading to withdrawal. Both of these patients were being treated with a comparator antiemetic combination. One patient suffered facial dyskinesia that started within one day of the start of study treatment and lasted one day when the event resolved. The other patient suffered facial dyskinesia while in the conditioning chemotherapy phase of the study; however, although being subsequently allocated to the TBI phase of the study, this patient never received antiemetic therapy for TBI.

In addition to the withdrawals due to AEs, during the conditioning chemotherapy phase of the study, 3 of 21 patients were withdrawn from the granisetron treatment group because of a lack of antiemetic efficacy. Similarly, there were also 4 patients from the comparator antiemetic group withdrawn because of a lack of antiemetic efficacy.

Sponsor's Conclusion(s)(Study 108)(Vol 10, pp 61-62)

The number of patients recruited into this study was considerably lower than the 112 patients (56 in each treatment arm) that had been originally planned. This is attributed to an important change in clinical practice that occurred while the study was in progress. The change consisted in giving TBI as a fractionated regimen over several days, rather than as a single dose administered in a single day. This resulted in an actual recruitment of only 39 patients.

The failure to recruit an adequate number of patients removed the possibility of performing any statistical analysis that might provide comparisons between groups.

The main focus of the present study was a comparison of granisetron with comparator antiemetic combination during TBI. Since the overall number of patients recruited in the study was well below that originally intended, this removed the possibility of any meaningful comparisons between the treatment groups. Informal comparisons revealed some minor differences between the treatment groups during TBI, although the proportion of patients who remained emesis-free as well as the time to first emesis were similar for both treatment groups.

For the TBI phases of the study, it was the clinician's opinion that the antiemetic treatments being used were qualitatively good or very good for 62.5% and 85.7% of the patients in the granisetron and comparator antiemetic groups. The numbers of patients in each treatment group, however, were too small to be sure of any treament differences. Two patients who were being treated with granisetron in the TBI phase and two who were being treated with a comparator antiemetic combination (chlorpromazine and metoclopramide) during conditioning chemotherapy were withdrawn from the study because of a significant adverse event. Two patients suffered transient facial dyskinesia, an extrapyramidal side-effect well known to occur with dopamine antagonist drugs such as chlorpromazine and metoclopromide.

There was only one death, due to multiorgan failure, which occurred in a patient who had been treated with granisetron during conditioning chemotherapy and then with a comparator antiemetic combination during TBI. In the investigator's opinion, this death was unrelated to study medication.

The sponsor concluded that the study failed in its main and secondary objectives of formally comparing the antiemetic efficacy of granisetron with comparator combinations during both TBI and conditioning chemotherapy. Although there were minor differences between treatment groups, the numbers involved were too small to allow any valid comparisons.

Reviewer's Comment: Although not explicitly stated in this section, it is apparent that the sponsor seeks use of the relevant patient data for study #108 in support of safety. This can be done because despite the differences in irradiation administration and granisetron dosage administration between and among the three studies, all patients from each of the differing studies can be used in the safety analysis with dose, duration, population, and other factors taken into account. It may be useful, nevetheless, to recount the differences between and among the three submitted studies. To start with, both the method of administration of the same radiation dosage as well as the dosage regimen by which granisetron was administered to patients in the first of the two studies (i.e., #259 and #448) differed in a major way from those in the present study (#108). In the first two studies of this submission, the dosage administration program consisted of 2 mg daily for the duration of the study (at least two weeks). In the other study (#448), the dosage regimen was daily over a four-day period, sufficient to allow delivery of three daily fractionated doses of Total Body Irradiation (total=11). In contrast, study #108 entailed delivery of the same amount of total irradiation

(about10Gy) over a single period of 4-10 hours. The dosage of granisetron given with this radiation delivery program was only 1 mg at the start of irradiation and 1 mg 12 hours later following its completion.

V. Overall Summary:

A. Efficacy of Granisetron:

The sponsor summarizes the data in support of the efficacy of granisetron in preventing radiation-induced nausea and vomiting related to fractionated upper abdominal radiotherapy in the sponsor's Volume 1: 83-99. The principal support for the claim of effectiveness is attributed to Studies #259 and #448 from which the sponsor concludes that 2-mg of granisetron taken as a single dose once daily is effective in the prevention radiation-induced nausea and vomiting.

Regarding study #259, from the data shown in Table 13 in this review, the sponsor believes that the median time (days) to first emesis in patients given granisetron tablets and Placebo - treated patients was 35 and 9 days, respectively. The Hazard Rate at endpoint was 1.89 (95% CI: 1.33, 2.67; $p<0.001$). The sponsor believes this difference between treatment groups, favoring granisetron is statistically significant. The same differences were evident for males and females, when gender was considered, although females tended to have a shorter time to emesis than males in both treatment groups.

The sponsor believes that when compared to the historical negative control group in study #448, a significantly higher proportion of patients who received granisetron tablets experienced no emetic episodes on Day 0 (first treatment day) (61.1%% vs 6.6%, respectively). Over the entire 4-day study period, these patients experienced a similar though less striking reduction in emesis (0% vs 33%, respectively). In addition, on granisetron they experienced complete emetic control (no emesis and no rescue medication over the entire 4-day study period (27.8% vs 0.0 %, respectively). A similar efficacy profile was observed in patients who received ondansetron tablets.

The reviewer believes that the efficacy of granisetron on emesis-control as shown in Table 7 at 24 hours and through the initial 10 of 20 fractions of fractionated upper abdominal irradiation in Study #259 is impressive and statistically significant. Although the effect seen at the full course of 20 fractions of radiotherapy has just missed the line of significance at $p=0.06$, there is more than one reason for this attenuation in response. The overall efficacy rate of 20-30% in treated patients over the placebo group for both emesis and nausea control is impressive in this study.

For study #448, there was initial concern over the discrepancies both in age and racial makeup between the two active treatment groups versus the historical negative control group. This concern was alleviated by the observation that these differences failed to make a difference, since all patients in this untreated group had very poor emesis- and nausea- control as shown in Table 20.

B. Safety of Granisetron:

The sponsor has divided the patient data into three different groups for safety analysis. Of the three groups, Population A comprised all patients in the three studies (#259, # 448, and #108) to make up a total of 326 patients. For reasons briefly discussed below, this was selected for analysis of safety. Population B that centered only on Fractionated Abdominal Irradiation and consists only of the 262 patients in Study #259, (134 patients who received granisetron and 128 patients who received placebo). Lastly, Population C was a selection of patients who received only Total Body Irradiation which consisted of 64 patients from Studies #448 and #108, both of which are described above under Population A.

Regarding adverse experiences in these clinical studies, the sponsor indicates that there were overall no remarkable differences between study groups (Population A) in the occurrence of adverse experiences. About 75% of patients who received granisetron, placebo, or comparative agents reported at least one adverse experience. The rate of adverse experiences reported for patients who received granisetron in the radiotherapy-induced population (79.8%) was comparable to that for patients who received granisetron 2 mg once daily (83.4%) in the chemotherapy-induced nausea and vomiting population as reported in the NDA 20-305/S-001 (Approved August 21, 1997). The sponsor indicates that the rate of occurrence of diarrhea (25.6%) was approximately 17% higher than that in the previously reported chemotherapy-induced nausea and vomiting studies, but the opinion is offered that this was likely related to the high incidence of diarrhea associated with upper abdominal radiotherapy and TBI. Notably, the incidence of diarrhea among placebo-treated patients was also high (34.4%) tending to support this explanation.

There were 17 patient deaths reported in the three studies. The data indicate that the majority of the deaths were reportedly due to progression of the primary disease or complications due to the primary disease. All of the deaths were considered "unrelated" to treatment with study medication. There were no clinically important differences between the treatment groups in the number or types of severe adverse experiences reported. None of the serious adverse experiences in any of the groups were reported as "possibly related" or "related" to treatment with study medication. There were also no clinically important differences between treatment groups in regard to the proportions of patients withdrawn for adverse events or in the types of adverse events resulting in withdrawal. A total of 20 (6.1%) patients were withdrawn from all studies.

The reviewer believes that assessment of the various types of possibly medication-related adverse events in relation to simultaneously-occurring other treatment events is difficult. The patients being treated are already afflicted with a grave, very likely life-threatening underlying problem, i.e., various types of cancer, lymphomas, and aplastic anemia. This situation is further compounded by the first line therapy administered for this, i.e., various forms of radiotherapy, which itself has a number of adverse effects. Superimposed on the above, questions are posed regarding potential adverse effects of granisetron, the indication for which is to help control very common and distressing immediate side effects of the radiotherapy. The

reviewer finds no serious reason to take issue with the presented, clinical-judgement-based observations of the sponsor, regarding safety issues.

For the present submission, the reviewer has adhered entirely to the data analysis of information obtained from population A. This because Population A is the largest group, comprises all three studies, and therefore most dilutes the potential impact on the analysis of data derived from differently treated patients in the distinctly different studies. For example, even in the two pivotal studies, the duration and intensity of both radiation therapy and granisetron administration were not comparable, i.e., four days in the TBI study (#448) vs one treatment daily on radiation days (about five times/week) for up to four weeks and often longer. The combined number of patients from studies #259 and #448 that are available for safety evaluation is 86+7=93 patients. The option of selecting Population A for a Safety analysis best serves to mitigate this potential problem.

VI. Reviewer's Overall Conclusions:

The data from the first of these three studies (Study # 259) demonstrates very convincingly that granisetron at a daily dose of 2 mg orally is effective and reasonably safe for prevention of nausea and vomiting associated with fractionated upper abdominal irradiation and hyperfractionated total body irradiation. Efficacy has been shown in the two pivotal studies, regardless whether the experimental design was placebo-controlled or whether appropriate historical negative controls were employed. No strikingly new concerns regarding Safety appear to have arisen form either of the two pivotal studies, dissimilar as they are or even with the addition of a small number of additional patients from study #108 (Population.A). In summary, the labeling requested by the sponsor in regard to both Total Body Irradiation and prolonged fractionated abdominal radiation seems warranted by the data presented in studies #259 and #448.

VII. Recommendations for Regulatory Action:

On the basis of the present data, it is recommended that:

1) Granisetron, 2 mg daily for four or more weeks, be approved for Radiation-induced Nausea and Vomiting. The dose should be administered one hour prior to radiation treatment over the period and duration of radiotherapy up to a maximum of six weeks.

2) Granisetron, 2 mg daily for four days, be approved for Hyperfractionated Total Body Irradiation prior to bone marrow transplantation. The dosage should be administered one hour prior to radiation treatment for the four days of this radiation program.

3) The sponsor's requested labeling changes (outlined below) seem appropriate for approval.

"[**Radiation-Induced Nausea and Vomiting**: *Kytril* Tablets, 2 mg daily, prevent nausea and vomiting associated with total body irradiation and fractionated abdominal radiation.

"***Total Body Irradiation:*** In a double-blind randomized study, *Kytril* Tablets, 2.0 mg daily, provided significantly greater antiemetic protection for patients receiving total body irradiation compared to patients in a historical negative control group who received conventional (non-5-HT_3 antagonist) antiemetics. Total body irradiation consisted of 11 fractions of 120 cGy administered over 4 days, with three fractions on each of the first 3 days, and two fractions on the fourth day. *Kytril* Tablets were given one hour before the first irradiation fraction of each day.]

"[Twenty-eight percent (28%) of patients treated with *Kytril* Tablets (n=18) did not experience vomiting or receive antiemetics over the 4-day dosing period, compared to 0% of patients in the historical negative control group (n=90) ($P<0.01$). Patients who received *Kytril* Tablets also experienced significantly fewer emetic episodes during the first day of radiation and over the 4-day treatment period, compared to patients in the historical negative control group. The median time to the first emetic episode was 36 hours for patients who received *Kytril* Tablets.]

"[***Fractionated Abdominal Radiation*:** The efficacy of *Kytril*, 2 mg daily, was evaluated in a double blind, placebo-controlled randomized trial of 260 patients. *Kytril* Tablets were given 1 hour before radiation, composed of up to 20 daily fractions of 180 to 300 cGy each. The exceptions were patients with seminoma or those receiving whole abdomen irradiation who initially received 150 cGy per fraction. Radiation was administered to the upper abdomen with a field size of at least 100 cm^2.

"Patients treated with *Kytril* Tablets (n=134) had a significantly longer time to the first episode of vomiting (35 vs. 9 days, $P<0.001$) relative to those patients who received placebo (n=126), and a significantly longer time to the first episode of nausea (11 vs. 1 day, ($P<0.001$). *Kytril* provided significantly greater protection from nausea and vomiting than placebo.]

"**Radiation-induced Nausea and Vomiting:**
In controlled clinical trials, the adverse events reported by patients receiving *Kytril* tablets and concurrent radiation were similar to those reported by patients receiving *Kytril* tablets prior to chemotherapy. The most frequently reported adverse events were diarrhea, asthenia and constipation. Headache, however, was less prevalent in this patient population.

"**Radiation (either Total Body Irradiation or Fractionated Abdominal Radiation):**
The recommended adult dosage of oral *Kytril* is 2 mg once daily. Two 1-mg tablets are taken within 1 hour of radiation.

"***Pediatric Use:*** *There* is no experience with oral *Kytril* in the prevention of radiation-induced nausea and vomiting in pediatric patients.

"***Use in the Elderly:*** *No* dosage adjustment is recommended."

/S/

R. Thomas Holzbach, M.D. 3-17-99 date

cc:
NDA 20-305/S-004
HFD-180
HFD-180/ L Talarico /S/ 3-29-99
HFD-180/ H Gallo-Torres
HFD-180/ T Holzbach
HFD-180/ J Choudary
HFD-181/ PM
HFD-180/ E Duffy
HFD-180/ M Al Osh
f/t 3/17/99 jgw
N/20305903.0TH

Noted. March 17, 1999

Agree with the main recommendation for approval of KYTRIL (granisetron hydrochloride) 1 mg tablets for the prevention of nausea and vomiting associated with the total body or fractionated abdominal radiation. Separate memorandum & NDA 20-305/SE1-004 follows.

/S/

APPEARS THIS WAY
ON ORIGINAL

VIII. References:

1. Hendriksson, R, et al: The effect of ondansetron on radiation-induced emesis and diarrhoea. Acta Oncologica 31: 767-769, 1992.
2. Priestman, TJ, et al: Clinical Studies with Ondansetron in the control of radiation-induced emesis. Eur J Cancer Clin Oncol 25: suppl 1: S29-S33, 1989.
3. Hunter, AE, et al: Granisetron, a selective 5-HT_3 receptor antagonist, for the prevention of radiation-induced emesis during total body irradiation. Bone Marrow Transplantation 7: 439-441, 1991.
4. Spitzer, TR, et al: Randomized double blind, placebo-controlled evaluation of oral ondansetron in the prevention of nausea and vomiting associated with fractionated total body irradiation. J Clin Oncol 12: 2432-2438, 1994.
5. Belkacemi,Y, et al: Total body irradiation prior to bone marrow tranplantation: Efficacy and Safety of Granisetron in the prophlaxis and control of radiation-induced emesis. Int J Radiation Oncol Biol Phys 36: 77-82, 1996.
6. Kris, MG, et al: Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. Cancer 78: 2193-2198, 1996.
7. Pocock, SJ: Problems with historical controls. In: Clinical Trials: A Practical Approach. John Wiley & Sons, New York, 1995; pp 54-60.
8. Diehl, AW: Gallstone disease in mestizo hispanics. Gastroenterology 116:1012-1015, 1998.

M 11e1

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 1999

FROM: Medical Team Leader
Division of Gastrointestinal and
Coagulation Drug Products (HFD-180)

APPEARS THIS WAY
ON ORIGINAL

SUBJECT: Secondary Medical Review:
KYTRIL® (Granisetron Hydrochloride), 1mg Tablets
Recommendation for Approval of Supplement SE1-004, submitted July 27, 1998: prevention of nausea and vomiting associated with total body irradiation (TBI) or fractionated abdominal radiation.

TO: NDA 20-305 (SmithKline Beecham Pharmaceuticals)

I. INTRODUCTION

APPEARS THIS WAY
ON ORIGINAL

Research in the 5-HT (serotonin) area has led to the development and approval of drugs for the prevention of chemotherapy-induced nausea and vomiting (N & V). These include: KYTRIL (granisetron•HCl), ANZEMET (dolasetron•HCl) and ZOFRAN (ondansetron•HCl, the first approved 5-HT_3 receptor inhibitor of this series). The latter is also approved for the prevention of post-operative N & V and for the prevention of N & V associated with radiotherapy.

Radiation therapy is an effective and routine treatment for a variety of malignant diseases[1]. The emetic stimulus from radiotherapy may be high (total body irradiation = TBI), moderately high (single high-dose fractions) or moderate (daily fraction) to the abdomen. TBI has commonly been incorporated into preparative regimens for bone marrow transplantation because of its potent myelosuppressive and immunosuppressive properties[2]. As pointed out by Spitzer et al [J. Clin. Oncol. 12: 2432-2438 (1994)] a major limitation of therapies for radiation-induced emesis, (RIE) has been N & V, which occurs in 30 to 83% of patients who receive upper abdominal or half-body irradiation and virtually in all patients subjected to TBI (MO review of NDA 20-103/SE1-004, ZOFRAN® TABLETS, for the prevention of RIE).

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[1] [S. Hellman. Principles of Radiation Therapy, in DeVita VT. Hellman, S. Rosenberg (eds.): Cancer: Principles and Practice of Oncology. Philadelphia, PA. Lippincott. 248-275 (1993)]
[2] [E.D. Thomas et al Int. J. Radiat. Oncol. Bio. Phys 8 :817-821(1982)
K.G. Blume et al. Blood 69: 1015-1020 (1987)
J.A. Brochstein et al. NEJM 317: 1618-1624 (1987)
T.R. Spitzer et al. Bone Marrow Transplant 4: 559-565 (1989)]

The sponsor 's supplement S-004 is in support of the use of granisetron hydrochloride (GRAN) 2-mg, as single daily dose to prevent N & V associated with radiation, including TBI and fractionated abdominal radiation. In support of their request, SK&B has submitted the results of these trials: one pivotal (US study #259) and two supportive (US study #448 and European study #108). The single blind, multicenter study #108 did not use an adequate design (see page 8 of the MOR of March 29, 1999) and was reviewed by neither the MO nor the statistician, by mutual agreement with the MTL. The recommendations for regulatory action are based on results of pivotal study #259, supported by results of study #448.

II. EFFICACY

Study 259 was double-blind, controlled, multicenter, used and adequate design and was apparently well-executed. Adult cancer naive patients with Karnovsky's performance status score of at least 60% who were scheduled to receive radiotherapy to fields encompassing vertebral levels thoracic 11 (upper border) with a field size of at least 100 cm^2 received either GRAN (n=138) or placebo (PL, n=126) prior to radiotherapy. Times of evaluation were at 24h, after administration of 10 fractions (ca. 2 weeks) and after administration of 30 fractions (ca. 6 weeks). Comments refer to results of evaluations of primary efficacy variables, namely complete emetic control, complete nausea controls, time to first episode of emesis, and time to first episode of nausea.

The efficacy results in this trial showed for the most part statistically significant comparisons in favor of KYTRIL (Table 1). Specifically, comparison at 24 h and after 10 fractions favored KYTRIL statistically; but after this point the effect was not statistically significant. The magnitude of the therapeutic gain decreased as more fractions of radiation (i.e. 20) were received. There is no plausible explanation for this finding but it may be due to **radiation-induced enteritis**. Using proportion of patients with emesis, the therapeutic gain (GRAN better than PL) was 31% at 24h ($p<0.0001$), 17% at 10 fractions ($p=0.0012$), 13% at 20 fractions (N.S.) and 15.4% overall ($p=0.0047$). Using proportion of patients with nausea, the therapeutic gain was 34% at 24h ($p < 0.0001$), 21% at 20 fractions ($p=0.0064$), 4% at 20 fractions (N.S.) and 14% overall 5 ($p=0.0042$). The median time to first emesis was 35 days for KYTRIL-treated patients in comparison to 9 days for those given PL (p-value for relative risk of 0.001). Furthermore, the median time to first nausea episode was 11 days for KYTRIL and 1 day for PL patients (p-value for relative risk < 0.001).

Table 1
NDA 20-305/SE1-004
Study #259

Treatment Response: Primary Efficacy Parameters
ITT Population

I. **Proportion of Patients with Emesis**

Time	GRAN		PL			
	n/N[a]	%	N/N[b]	%	Therapeutic Gain	p=Value
24h	10/34	7.5	48/126	38.1	-30.6%	<0.0001
10 Fractions	15/104	14.4	23/74	31.1	-16.9%	<0.0012
20 Fractions	12/52	23.1	13/36	36.1	-13%	NS
Overall	57/134	42.5	73/126	57.9	-15.4%	0.0047

II. **Proportion of Patients with NO NAUSEA**

Time	GRAN		PL			
	n/N[c]	%	n/N[d]	%	Therapeutic Gain	p=Value
24h	106/134	79.1	57/126	45.2	+33.9%	<0.0001
10 Fractions	55/104	52.9	24/74	32.4	+20.5%	<0.0064
20 Fractions Total	18/52	34.6	11/36	30.6	+4%	NS
Overall	41/134	30.6	21/126	16.7	+13.9%	0.0042

III. **Time to First Episode of Emesis**

Median time (Days)				
GRAN [n=134]	PL [n=126]	Hazard (Risk) Rate	p-Value for Relative Risk	95% Confidence Intervals for Risk Ratio GRAN vs PL
35	9	1.89[e]	<0.001	(1.33,2.67)

IV. **Time to First Episode of Nausea**

Median time (Days)				
GRAN [n=134]	PL [n=126]	Hazard (Risk) Rate	p-Value for Relative Risk	95% Confidence Intervals for Risk Ratio GRAN vs PL
11	1	1.78[f]	<0.001	(1.34,2.36)

This Table is a composite from MOR Tables 9. 10, 11 and 12 with modifications introduced by the MTL.
a through d) n=number of patients affected; N=total number of patients at risk
e) Indicates that the chance of **emesis** occurring in the untreated group is about <u>double</u> that for the treated group.
f) Indicates that the chance of **nausea** occurring in the untreated group is about double that for the treated group.

Study 448 was a double-blind, double-dummy, randomized, active-active multicenter trial. The objective of the study was to compare the proportion of patients with no emetic episodes of each of two active treatments, Kytril Tablets 2 mg once daily and overencapsulated Ondansetron Tablets 8 mg three time daily, in patients receiving hyperfractionated TBI to that of a historical control group. The study population consisted of adult cancer or aplastic anemia patients who were radiation-naive. The primary efficacy endpoint was complete emetic control over the entire 4-day study period. The original protocol explicitly stated no intent to demonstrate comparability in efficacy for the two antiemetic treatment groups. The experimental treatment groups (total n=33) were of inadequate size to demonstrate superiority via a head-to-head comparison. Although there were some constraints, all in all, the historical control used by the sponsor was relevant. Explanations on sample size calculations (sponsor's submission of May 19, 1999) and number of patients with efficacy results are given in the statistician's review (pages 18 and 19 of Dr. M. Al-Osh review of June 7, 1999). The total n in the historical control was 90.

In study #448, a total of 34 (18 received KYTRIL and 16 received ondansetron) patients were enrolled in the trial. According to the sponsor calculations, the proportion of patients with no emetic episodes over the entire 4-day study period and with complete Emetic Control was:

	GRAN	OND
No Emetic Episodes Over 4-day Study	6/18 (33.3%)[a]	4/15 (26.9%)[b]
99% CI	(6.4, 69.2)	(0.9, 67.3)
Complete Emetic Control	5/18 (27.8%)[c]	4/15 (26.7%)[d]
99% CI	(2.9, 64.3)	(0.9, 67.3)

a through d $p<0.01$ when compared to historical control [0/90 = 0% for both endpoints]

According to the FDA statistician's analysis, 4/18 (= 22.2%) of the KYTRIL-treated patients were emesis free during the entire 4-day study period (instead of the 6/18=33.3% calculated by the sponsor). As pointed out on page 21 of the FDA statistician's review, the 99% CI of the difference between Kytril and the historical control response rates included the value zero. This contrasted with the sponsor's analysis since according to SK&B evaluations, the 99% CI of the difference between Kytril and the historical control did not include zero. However, as shown above these CIs were **wide** due to the small n in the Kytril group. Nonetheless, the MTL believes that the results of study #448 do support those of the pivotal trial #259.

III. SAFETY

The safety experiences with GRAN patients receiving radiotherapy arises from relatively few observations: 134 patients in study 250, 18 in study 448 and 16 in study 108. This represents a total n of 168. The majority of the 17 deaths occurring during the three trials were due to progression of or complications due to primary disease. None of the SAEs in any of the groups were assessed as related to test medication and there were no important differences between granisetron and comparators in the number or types of severe AEs reported. The rate of AEs reported for patients who received GRAN in the radiotherapy-treated population (79.8%) was comparable to that for patients who received GRAN 2 mg once daily (83.4%) in the chemotherapy-induced N & V population as reported in the NDA 20-305/S-001 (Approved August 21, 1997). The rate of occurrence of diarrhea (25.6%) was ca. 17% higher than that in the previously reported chemotherapy-induced N & V studies. This was likely due to the high incidence of diarrhea associated with upper abdominal radiotherapy and TBL (**"radiation-induced enteritis"**) since the incidence of diarrhea among placebo-treated patients was also high (34.4%). In summary, the available, limited data suggest that GRAN at the daily oral dose of 2 mg administered to patients receiving radiotherapy regimens is reasonably safe and well-tolerated. Except for higher incidence of diarrhea, most likely due to the radiotherapy, this safety information appears to be similar to that previously seen when the drug was administered to other patient populations for which the compound has been approved, such as chemotherapy-induced emesis.

IV. RECOMMENDATIONS FOR REGULATORY ACTION (RFRA)

Based on results of pivotal study #259, supported by those of study #448, the following is recommended.

1. Approval of granisetron, 2 mg daily for up to 2 weeks (up to 10 fractions) for the prevention of radiation-induced nausea and vomiting.

   The prophylactic dose of the drug should be administered one hour prior to radiation treatment over the period and duration of radiotherapy up to a maximum of 10 fractions (approximately 2 weeks).

2. Approval of granisetron, 2 mg once-a-day for four days for the prevention of nausea and vomiting associated with hyperfractionated TBI prior to bone marrow transplantation.

   The prophylactic dose of the drug should be administered one hour prior to radiation treatment over the four days of this radiation program.

3. Matters related to the proposed labeling are being addressed separately, in conjunction with Ms. Kati Johnson, Supervisor Project Manager.

It is to be noted that the MTL's recommendation for regulatory action No. 1 **differs** from that of the MO. In his RFRA the MO does not clearly specify whether the indication is for prevention or treatment of RIE. Also, the MO recommends that the 5-HT_3 receptor antagonist be administered over the period and duration of therapy, **up to 6 weeks**. However, based on the evidence summarized in Table 1 of this review, after 10 fractions (approximately 2 weeks) the effects with granisetron could not be differentiated from those with placebo.

June 18, 1999
/S/
Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-305
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F/t 6/18/99 jgw
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APPEARS THIS WAY
ON ORIGINAL