CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020305/S004

MEDICAL REVIEW(S)

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S NEW DRUG APPLICATION (NDA) REVIEW

NDA	20-305/SE1-004
Sponsor:	SmithKline Beecham Pharmaceuticals Philadelphia, PA 19101
	MAR 29 1999
Drug:	Granisetron hydrochloride (KYTRIL®), 1 mg Tablets
Pharmacological Category:	Antiemetic/Antinausea Antagonist of 5-OH-Tryptamine Receptors
Route of Administration:	Oral
Dose:	1.) Two mg once daily prior to total body irradiation over 4 days prior to bone marrow transplantation and 2.) Two mg once daily prior to upper abdominal radiation for up to the time required to receive 20 fractions of radiotherapy.
Proposed Indication:	Prevention of nausea and vomiting associated with total body irradiation or fractionated abdominal radiation
Important Related Drug:	Ondansetron (Zofran®)
Date Submitted:	July 27, 1998
Date of Drafts:	January 25, 1999, February 9, 1999, March 1,1999
Material Reviewed:	Submitted on July 27, 1998: Application, Volumes 1-20 (of 37 Volumes); containing clinical material, proposed labeling; pertinent other information and references. Three protocol amendments dated: 22 April 1996 (#1), 30 April 1996(#2), and 29 July 1997(#3) were indicated. Submitted on August 26, 1998: Amendment, a hardcopy of comprising Volumes 1-17R of Items #11 and #12 that were originally submitted in electronic format; This included supplementary Patient ID's and Case Report Forms. Submitted on September 1, 1998: Amendment, Appendix 1a for Study 259 ("List of Investigators")(Vol. 4) Submitted on October 22, 1998: Amendment, including attachments # 1-4, covering notably in #3 a description of how randomization was carried out, including how patient numbers were assigned, and a copy of the computer generated randomization code.
Medical Reviewer:	R. Thomas Holzbach, M.D.

Brief Overall Submission Synopsis

Granisetron is a potent and selective 5-HT_3 receptor binder and inhibitor. It has previously been approved for therapy of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high dose cisplatin, at a dose of 1mg/day. SmithKline Beecham is requesting that its tablet formulation of granisetron (Kytril®) two 1 mg tablets once daily, one hour prior to radiation on radiation days and at the same time of day on "rest" (non-radiation) days be approved. The indication sought is for prevention of nausea and vomiting in cancer patients prior to: a) fractionated total body irradiation; b) bone marrow tranplantation for aplastic anemia, lymphomas, and related diseases. Approval is also sought for prevention of nausea and vomiting associated with fractionated upper abdominal irradiation for other cancers, principally genitourinary and gastrointestinal tract cancers, and for lymphomas. In support of this, the sponsor has submitted three studies, two of which (#259 and #448) are pivotal. They were USA randomized controlled multicenter clinical trials. The third supporting study (#108) was conducted in five European centers according to a different radiotherapy and antiemetic medication regimen. This involved a single blind, single arm study of a limited number of patients. The two pivotal studies show that granisetron in a dose of 2 mg 1 hour prior to irradiation is reasonably safe and effective in the prevention nausea and vomiting associated with two forms of radiation-induced nausea and vomiting, i.e., total body irradiation and fractionated abdominal radiation. Accordingly, in the recommendations for regulatory action section, the reviewer indicates that the labeling changes requested by the sponsor seem appropriate.

MEDICAL REVIEW OF NDA 30-305/ S-004
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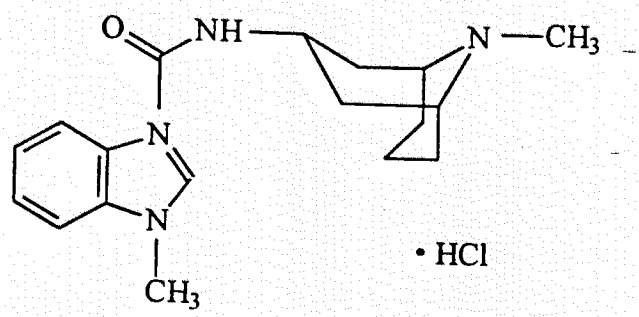
I. Background/Introduction:

A. Description of the Drug

Granisetron hydrochloride is chemically endo-N- (9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamine hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O \cdot HCl$. Its chemical structure is indicated below.



Granisetron Hcl

Granisetron is available in 1-mg tablet and injection dosage forms for the indication of prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. Each white triangular, biconvex, film-coated, ***Kytril*** Tablet contains 1.12-mg granisetron hydrochloride equivalent to granisetron 1 mg. Inactive ingredients are: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide in its formulated product form.

B. Clinical Pharmacology

According to the presently approved labeling, which is quoted verbatim from Vol. 1, pp 44-46 of the sponsor submission, "Granisetron is a selective (5-HT_3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT_1; 5-HT_{1A}, 5-$HT_{1B/C}$,; for alpha$_1$-, alpha$_2$-, or beta-adrenoreceptors; for dopamine-D_2; or for histamine-H_1; benzodiazepine; picrotoxin, or opioid receptors.

"Serotonin receptors of the 5-HT_3 type are located peripherally on vagus nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT_3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5 to 30 seconds.

"In most human studies, granisetron has had little effect on blood pressure, heart rate, or ECG. No evidence of an effect on blood prolactin or aldosterone concentrations has been found in other studies. Following single and multiple oral doses, Kytril slowed colonic transit in normal volunteers. However, Kytril had no effect on oro-cecal transit time in normal volunteers when given as a single intravenous (IV) injection infusion of 50 mcg/Kg or 200 mcg/Kg.

"Pharmacokinetics:

"In healthy volunteers and adult cancer patients under going chemotherapy, administration of Kytril produced the following mean pharmacokinetic data:

Pharmacokinetic Parameters (Median [range]) following Oral Kytril (granisetron hydrochloride)

	Peak Plasma Concentrations (ng/ML)	Terminal Phase Plasma Half-Life (h)	Volume of Distribution (L/kg)	Total Clearance (L/h/kg)
Cancer Patients 1.0 mg bid, 7 days (n=27)	5.99 [0.63 to 30.9]	N.D.*	N.D.	0.52 [0.09 to 7.37]
Volunteers single 1.0 mg dose (n=39)	3.63 [0.27 to 9.14]	6.23 [0.96 to 19.9]	3.94 [1.89 to 39.4]	0.41 [0.11 to 24.6]

* not determined after oral administration; following a single intravenous dose of 40mcg/kg, terminal phase half-life was 8.95 hours.
*N.D. Not Determined

"The effects of gender on the pharmacokinetics of oral kytril have not been studied. However, after intravenous administration of kytril, no difference in mean area under the curve (AUC) was found in males and females, although males had a higher C_{max} generally.

"When oral kytril was administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

"Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Animal studies suggest that some of the metabolites may also have 5-HT_3 receptor antagonist activity.

"Clearance is predominantly determined by hepatic metabolism. In normal volunteers, approximately 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

"*In Vitro* liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily.

"Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells."

C. Brief Background of previous NDA for granisetron (Regulatory History)

The initial NDA for granisetron tablets was approved on March 16, 1995 for the indication of prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin, at a dose of 1 mg/day. The indications were the same as for the previously approved (S-001) dosage regimen (1 mg in two divided daily doses = 1 mg BID). Subsequent submission of supplement S-003 led to approval on June 8, 1998 of a 2 mg/day (two 1 mg tablets) in a single dose for the same indication. The last amendment to supplement S-001 was approved for the purpose of using 2 mg as a single daily dose prior to chemotherapy. The present supplement S-004 is in support of the use of granisetron 2-mg, as a single daily dose to prevent nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

D. Requested Labeling for New Indication

SmithKline Beecham proposes to revise this section of the package insert to add the following new indication and usage. The additional language requested is:

"INDICATIONS AND USAGE:
Kytril (granisetron hydrochloride) is indicated for the prevention of:

[nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.] This labeling information in quotes or brackets is verbatim from the sponsor's submitted Vol. 1, p 51.

In support of their request, the sponsor has submitted the results of the three trials, number of patients in each study, main features of study designs, and other related material that is summarized in Table 1.

Table 1
Summary of Studies

Study Identification	Main Design Features	Study Population	Groups Being Compared	Remarks
A. Study 259; BRL- 43694/ RSD-100JSK/2 (n= 260) ITT population (USA)	Double blind, placebo-controlled, randomized, multicenter (n=38). Primary efficacy parameter was time to first emesis during the time required to receive up to 20 radiotherapy fractions.	Adult (≥18y) male or female cancer patients, radiation naive, with Karnovsky performance status score of at least 60% Scheduled to receive radiotherapy to fields encompassing vertebral levels Thoracic 11 (upper border) through Lumbar 3 (lower border) with a field size of at least 100 cm^2 Scheduled to receive at least 10 and no more than 30 fractions of radiotherapy	Granisetron prior to radiation on radiation days and at same time on non-radiation days (n= 134) population. vs. Placebo, once daily, 1h prior to radiation on radiation days and at same time on non-radiation days (n= 126) population. Duration of study was the time required to receive at least 10 radiation fractions (about two weeks) and the time required to receive no more than 30 radiation fractions (about six weeks)	• Useful design (experimental vs placebo comparison) • Modified Intent-to Treat Analysis based on exclusion of four patients who were randomized • Novel primary efficacy endpoint of "time to first emesis" used in study conducted over weeks rather than days • Ratio of males/females is 1.9.
B. Study 448; BRL-43694A (n=33) ITT population (USA)	Double blind, double dummy, randomized, active-active, multicenter; Primary efficacy Endpoint was complete emetic control over entire 4-day study period. Efficacy and Safety were assessed over 4 days during which a total of 11 fractions consisting of 120 cGy each for a total of 1320 cGy radiation exposure. Medication dosage schedule outlined in Table 18.	Adult (≥18y) M or F cancer or aplastic anemia patients , radiation-naive and with none of the following: intrathecal chemotherapy Within 24 h of the first fraction of irradiation on day 0; no emetogenic, systemic or intrathecal chemotherapy concomitantly during the course of the study.	Granisetron 2 mg, once daily, 1h prior to receiving the first fraction of radiation on day 0 through day 3 population (n=18). vs. Overencapsulated ondansetron tablets 8 mg 1.5 h prior to each fraction of radiation on day 0 through day 3 (n=15) population Historical negative control group of 88 pts untreated with 5-HT_3 receptor antagonists for nausea and vomiting.	• Useful design • Design effectiveness depends entirely on use of historical controls for demonstration of efficacy. • Use of historical controls under circumstances of present study appears acceptable • Original protocol explicitly states no intent to demonstrate comparability in efficacy for the two antiemetic treatment groups • Experimental treatment groups too small individually to permit a potential superiority via a head-to-head comparison

Table 1-Summary-Cont.

Study Identification	Main design Features	Study Population	Groups Being Compared	Remarks
Study 108: BRL 43694A Additional supporting Study (n=30) (European)	Single Blind, Multicenter (five). Patients randomized initially to conditioning chemotherapy and randomized treatment with either granisetron vs active comparator combination, e.g. chlorpromazine plus metochlopramide. This was to have been carried out for a period of about one-week followed by administration of Total Body Irradiation. Note: the amount of irradiation administered (10 Gy) was equivalent to that given in Studies #259 & #448, but it was given entirely as a single dose over a 4-10 hr period. Granisetron was given in dosage of 1 mg at the start of TBI and 12 hrs later following its completion. Primary Efficacy Parameter was no emesis over 24 hrs. Multinational: France & Sweden	Patients with conventional indications for and eligible for TBI, including various forms of cancer, aplastic anemia, etc.	Patients were randomized twice. First to conditioning chemotherapy with either granisetron or a comparator combination. Next, those patients completing this phase were re-randomized before follow-up TBI and treatment with either granisetron or with comparator combination. Of the 30 patients randomized to TBI after conditioning chemotherapy, 16 patients received granisetron.	• Not a useful design. This is because administration of both total body irradiation and dose of study medication is not comparable to that of second pivotal study (# 448) • Small numbers of patients in each of the two active treament groups during TBI precludes efficacy analysis and makes even safety analysis problematical for comparison with Study # 448

(Table 1-Summary of Studies was prepared by the reviewer.)

II. Study #259 (Start date: June 1996-Completion date: October 1997)

"A Double-Blind, Parallel Multicenter Study Comparing the Safety and Efficacy of Kytril® (granisetron hydrochloride) Tablets 2 mg Once Daily With Placebo in The Prophylaxis of Nausea and Vomiting In Patients Receiving Fractionated Upper Abdominal Radiotherapy for Malignancy."

1. Objective(s) (as listed by the sponsor)

(1) To compare the efficacy for preventing nausea and vomiting, granisetron tablets 2 mg were administered once daily versus placebo in patients receiving at least 10 (maximum of 20 fractions utilized for efficacy and safety assessments) fractions of upper abdominal radiation. These were principally for malignancy of the genitourinary and digestive tracts together with lymphomas.

(2) To assess the safety of granisetron tablets 2 mg once daily given for up to the time (approximately 4 weeks) required to receive 20 fractions of radiation.

2. Study Design (as outlined by the sponsor)

This was a randomized, double blind, parallel-group, placebo-controlled, multicenter study. Patients were screened for eligibility within one week before the first scheduled day of radiation. The study was conducted for the period of time required to receive at least 10 (two weeks) and no more than 30 fractions of radiation (about 6 weeks based on 5 fractions/week). On the first day of radiation, patients were randomized to receive granisetron tablets 2 mg (two 1 mg tablets) or two placebo tablets that were to be taken each day for the duration of their participation in the study. Patients returned for a follow-up evaluation within 9 days of the last dose of study medication and radiation treatment.

The sponsor notes that there were three study amendments, the first two of which were initiated before the first patient was enrolled in the study, which allowed, for example, for the inclusion of patients with seminoma (Amendment 2), but overall did not alter the character of the study. The third amendment provided for the exclusion of patients who were scheduled to receive wedge field radiation to the spine or prophylactic radiotherapy to the central nervous system. The revision was made because such therapies are not emetogenic and, therefore, not suitable for this study. Although this amendment was introduced about the midpoint of the duration of the study, its introduction was not considered predjudicial to the fundamental design or outcome of the study. It is unspecified how many patients were affected by this amendment.

3. Study Population (from the sponsor)

As indicated in Table 2, the criteria for inclusion were acceptable for this type of study.

Table 2

Characteristics of the Study Population (Study 259)

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Adults (≥ 18y) cancer patients (of both genders and principally of the types indicated above); • Signed Informed Consent Form; willingness and ability to comply with the protocol requirements; • Scheduled to receive at least 10 and no more than 30 fractions of radiotherapy; • Scheduled to receive radiotherapy to be given to fields encompassing the upper border of the 11th thoracic (T11) through the lower border of the third Lumbar (L3) vertebrae, with a field size of at least 100 cm^2; • Scheduled to receive the acceptable dose of radiation; consisting of at least 180 cGy per fraction up to 300 cGy per fraction, with a total weekly dose of at least 900 cGy (except for patients with seminoma who could receive lower fractional doses and lower total weekly doses of radiation); • Must not have received radiation within 24h before day 0 (the day of randomization and the first dose), nor any *emetogenic chemotherapy* within 72h of study medication or during the period of study; • Males must have been surgically sterilized or agreeable to practicing adequate contraceptive precautions during the study; • Females must have been of non-childbearing potential (i.e., those who have been surgically sterilized, or who are at least one-year post-menopausal). Females of childbearing potential must have had a negative pregnancy test (urine or serum hCG) before entry into the study, and must have agreed to practice adequate contraceptive precautions.	• 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; • Unstable medical disorder; • Karnofsky (a performance activity classification) performance status score of <60; • Receipt of chronic (1 month or more) or concurrent (day 0 and through the end of assessment) treatment with agents known to have a significant effect on emesis (e.g., ondansetron, sedating antihistamines, metoclopromide, benzodiazepines, corticosteroids, cannabinoids, narcotic analgesics, etc.); • Primary or secondary (from metastatic disease) brain tumors with signs or symptoms of increased intracranial pressure; • Known to be hypersensitive to any 5-HT3-receptor antagonist; • Unwilling or unable to comply with protocol; • Must not have received emetogenic chemotherapy within 72h of administration of study medication, nor have been scheduled to receive emetogenic chemotherapy during the assessment period of the study; • Must not have received abdominal radiotherapy (T-11, L-3). They must not have been scheduled to receive wedge-field radiation therapy to the spine, or prophylactic therapy to the central nervous system. They must not have received any radiation therapy within 24 hours before Day 0; • Must not have had any nausea within 1h and/or emesis (vomiting and/or retching) within 24h before dosing with study medication on Day 0.

(Table devised by Reviewer from sponsor's information)

4. **Highlights of Study Execution; Efficacy Assessment** (sponsor's description)

- On the first day of radiotherapy (Day 0), eligible patients were randomized to receive a dose of either two granisetron tablets (two 1 mg tablets) or two placebo tablets. Study medication was to be ingested one hour before the start of radiotherapy. Thereafter, coded medication was to be given each day, at the same approximate time, for the full duration of the study (the time required to receive 20 fractions of radiotherapy = about 4 weeks).

- Efficacy Endpoints: The efficacy Endpoints were all recorded for the time period required to receive up to 20 radiotherapy fractions.

- The **Primary efficacy Endpoints** were:
  (a) Time (days) to first emesis
  (b) Time to first nausea.

For both variables, if this comparison was significant, additional comparisons were to be made at 24h after 10 fractions and after 20 fractions of radiotherapy.

- The **Secondary Efficacy Endpoints** were:
  (a) Proportion of emesis-free days
  (b) Number of emetic episodes
  (c) Proportion of nausea-free days, and
  (d) Proportion of "None"/"Mild" grade days (note: in the protocol, this is the only attempt to employ a qualified description of severity of nausea)

Reviewer's comment: This use of a different time-dependent primary endpoint other than "complete response" for the present study is noted. This is used in the succeeding study #448 of this submission and in previous submissions leading to approvals for use of this class of antiemetic agents, e.g., granisetron for chemotherapy-N&V, ondansetron for radiation-induced N&V. Since the present protocol is of several weeks' duration as compared to 4 days for TBI studies, it must surely be that this is duration difference explains the change in efficacy endpoint chosen for this study. Considering the much greater length for both irradiation and granisetron treatment exposure in the present study, the present change in endpoint seems reasonable to this reviewer.

5. **Test Medication/Maintenance of blinding** (sponsor's description)

- To maintain the double-blinded character of the trial, each patient received two similar tablets at the same time study drug was administered 1 hour prior to radiotherapy on radiation and at the same time on non-radiation days. Random assignment to one or the other of the two groups was according to a computer-generated randomization schedule prepared by the sponsor before the start of the study. **(Reviewer's note**: Both the sponsors computer-generated randomization results and its distribution to the various participating centers was carefully checked and validated).

- Blinded test medication was packaged in amber glass bottles containing 20 tablets per bottle.

- Granisetron and placebo tablets were identical in appearance.

6. **Statistical Methodology** (sponsor's description)

- Power calculation: It was estimated that 300 patients would be needed to detect a 20% treatment difference between granisetron and placebo groups with an $\alpha = 0.05$, 2-sided level of significance and 90% power test. This was based on the assumption that the granisetron group treatment effect would be 40% (N.B. primary efficacy endpoint of time to event is not involved in this calculation).

- The protocol-based primary efficacy analysis for the comparison of oral granisetron 2 mg tablets versus placebo (regarding the time [days] to first emesis and time [days] to first nausea) was to be performed using Cox Proportional Hazard Regression methodology via the SAS system procedure. If rescue antiemetic was taken in the absence of emesis, time to rescue would be considered equivalent to time of first emesis. If rescue emesis were taken in the absence of nausea, time to rescue would be considered equivalent to time of first nausea.

- If the overall treatment was found to be significant from the Proportional Hazards model, three individual time points would be tested: 24h, 10 fractions (2 weeks) and 20 fractions (4 weeks).

- The following secondary efficacy endpoints were to be analyzed as follows:

  a) The proportion of emesis-free days and b) the proportion of nausea-free days were to be compared between the two treatment groups using Wilcoxon rank sum test stratified by center. Proportion of emesis-free days and proportion of nausea-free days were to be calculated by dividing the number of emesis-free days or nausea-free days for a patient by the number of days the patient was on study medication, regardless of whether or not a patient received rescue antiemetic.

  b) The number of emetic episodes was to be analyzed using Wilcoxon rank sum test adjusting for the length of anti-emetic treatment and for center. Adjustment for length of anti-emetic treatment was to be done by dividing the number of emetic episodes by the number of days on treatment. Use of rescue antiemetic was not considered in this analysis.

  c) Proportions of "None"/"Mild" nausea grade days were to be compared between the two treatment groups using Wilcoxon rank sum test stratified by center. Proportion of "none"/"mild" nausea grade days was to be calculated by dividing the number of "none"/"mild" grade days for a patient by the number of days the patient was on study medication, regardless of whether or not a patient received rescue medication.

Further, a comparison between treatment groups for the proportion of emesis-free patients, nausea-free patients, or patients with "none"/'mild" nausea grade days on at least 80% of days on study was to be performed using the Cochran-Mantel-Haenszel test.

According to the sponsor's original protocol, "An intent-to-treat (ITT) analysis was to be performed. This would include all patients who were randomized and received study medication and had at least one post-dose assessment. However, prior to unblinding the study, the database was to be reviewed for significant protocol violations, which might affect efficacy evaluability. If warranted by this review, an efficacy evaluable population that excludes patients with significant protocol violation, would also be analyzed (protocol-defined analysis)". The outcome of this procedure is outlined in Table 3.

Reviewer's comment: The sponsor's description on ITT is unclear. For more opinion on this point see the commentary below immediately following Table 3.

7. **Results** (sponsor's description)

(a) **Participating Investigators/Patient Accounting**

- 45 investigators at 38 centers within the USA conducted the study.
- Of 297 patients screened for entry, 33 patients failed screening because of inability to meet inclusion criteria.

Table 3

Number of Patients Screened, Randomized, and Evaluable for Efficacy Analysis

Number of Patients	Granisetron	Placebo	Failed Screening	All Patients
Screened				297
Randomized*	134	130	33	264**
Evaluable for Intent-To-Treat Analysis (ITT)	134	126**	-	260
Evaluable for Protocol Defined Analysis (PDA)	96	90	-	186

(from sponsor's table 3, Vol 4, p 46) Section 4. Study Population (also from Appendices 1b, 2b, and 3)
** Four patients were randomized but not included in the ITT population because they did not receive study medication and/or radiation or did not record any efficacy assessments. The four patients who were randomized but excluded from further analysis included the following: # 259.037.8615-who received no antiemetic or irradiation; #259.052.8586-who died prior to screening conclusion on day 0; #259.043.0111-who received one day of radiation and then withdrew for lack of efficacy; and #259.048.0280-who underwent irradiation treatment for one week, failed emetic and nausea control, and took rescue medication. This information was obtained from Appendix 2 (a) Vol 2R); (none of these patients were from the same treatment center, and all had been randomized to placebo-Source: Amendment #4- October 25, 1998, data on randomization by center from the sponsor)

Reviewer's Comment: This difference of four patients having been excluded (modified ITT) only from the randomized ITT placebo group fails to reach statistical significance by the Fisher Exact Test. In the sponsor's originally submitted protocol, the words describing the plan was ambiguous in that the following language was used,"an intent-to-treat analysis will be performed. This includes all patients who were randomized and received study medication. and had at least one post-dose assessment"

- The remaining 260 patients were randomized to study drug, and thus were the population (ITT population) available for assessment of safety

(b) **Withdrawals/Completed Patients**

As indicated in Table 4, the numbers of patients withdrawn due to AE's or protocol violations were similar between the Treatment and Placebo groups.

Table 4

Number and Percent of Randomized Patients who Completed the Study Or who were Withdrawn

Final Study Status And Withdrawal Reason	Granisetron (N= 134)	Placebo (N= 130)
	n (%)	n (%)
COMPLETED STUDY*	**86 (64.2)**	**57 (43.8)**
WITHDRAWAL REASON		
Adverse Experiences	11 (8.2)	8 (6.2)
Lack of Efficacy/ Use of Rescue Medication	30 (22.4)	56 (43.1)
Deviation from Protocol/Non-Compliance	4 (3.1)	4 (3.1)
Loss to follow-up	1 (0.7)	2 (1.5)
Other Reasons	2 (1.5)	3 (2.3)
TOTAL WITHDRAWN	**48 (35.8)**	**73 (56.2)**

*Completed patients are those who took at least 80% of prescribed doses for the period of time required to receive 20 fractions of radiation. Data recorded by research nurses at treatment sites on CRF forms on treatment days and recorded on worksheets by the patients on non-treatment days. Patients also had to have attended follow-up visit. (Reviewer's note: the Reviewer has verified Each of the numbers in the above two columns above in Table 4. There was no unusual clustering or imbalance that occurred from contributions from any single center.)
(Data obtained from sponsor's sources, including Table 4-Vol.4, p.47, Table 2-Vol 5, pp.7-8, Appendix 2a [Vol 2R] and Appendix 26 [Vol 9R])

As noted by the sponsor, withdrawals due to Lack of Efficacy (or use of rescue antiemetics) were, however, much more numerous in the Placebo group (56 patients or **43.1%**) than in the Treatment group (30 patients or **22.4%**). The discrepancy accounted for the disparity of **29** fewer patients in the Placebo group who completed the study (**57** patients) versus the Treatment group (**86** patients).

(c) **Protocol Violations**

The Protocol-Defined analysis excludes all patients with documented protocol violations thought to compromise the assessment of efficacy.

According to the sponsor, a blinded review of relevant patient data identified 90 protocol violations in a total of 78 (29.5%) patients in the Intent-To-Treat population. The sponsor states that 38 (28.4%) patients who received granisetron were excluded for 41 protocol

violations. Forty (38.8%) patients in the placebo group were excluded for 49 protocol violations. This review identified all violations that occurred for each patient during the study.

The number of patients and reason for exclusion from the Protocol-Defined Analysis is given in Table 5.

Table 5

Number of Patients Excluded from Protocol-Defined Analysis and Reason for Exclusion

Protocol Violation	Granisetron (n=134)	Placebo (n=130)	Total (n=264)
Less than 80% compliance in use of study medication	7 (5.2)	8 (6.2)*	15 (5.7)
Missing nausea and/or emesis assessments	14 (10.4)	13 (10.0)	27 (10.2)
Non-seminona/ whole abdominal radiation patients who received <180cGy/fraction or >300 cGy/fraction	3 (2.2)	4 (3.1)	7 (2.7)
Received benzodiazepine within 8h of radiation	1 (0.7)	1 (0.8)	2 (0.8)
Received antiemetic rescue medication during treatment but did not withdraw	0	1 (0.8)	1 (0.4)
Received no radiation	0	3 (2.3)	3 (1.1)
Received prohibited medication(s)	5 (3.7)	13 (10.0)	18 (6.8)
Seminoma patients who received <150 cGy/fraction**	11 (8.2)	6 (4.6)	17 (6.4)
Total Number of Protocol Violations	**41**	**49**	**90**
Total Number of patients with Protocol Violations	**38 (28.4%)**	**40 (30.8)**	**78 (29.5)**

* Two patients who were randomized but received no study medication are included. **The lower limit of radiation dosing was established as a violation after study completion, but before unblinding. Note: A given patient may have been excluded for more than one reason. (Modified from sponsor's table 6, Vol 4, p 49)

(d) **Comparability of Groups/Patient Baseline Characteristics**

As indicated in Table 6, the most frequently occurring cancers affecting the patients in this study **(i.e., 40-50%)** were cancers of the genitourinary system. Specifically, the largest sub-group in this category of patients included 27 (19.6%) patients in the granisetron-treated group and 15 (11.8%) in the placebo group with various forms of seminoma.

Table 6

Demographic and Baseline Disease Characteristics

	Granisetron (n=134)	Placebo (n=130)
A. Demographics		
Male	87 (64.9%)	85 (65.4%)
Female	47 (35.1%)	45 (34.6%)
Mean Age (y)	53.6	55.4
Range (+ SD) (y)	17.7	17.2
Race		
Caucasian	106 (79.1%)	101 (77.7%)
Black	14 (10.4%)	14 (10.8%)
Oriental	1 (0.7%)	3 (2.3%)
Other	13 (9.7%)	12 (9.2%)
B. Primary Tumor Site		
Genitourinary	50.7%	40.0%
Lymphoma/ Hematologic	20.9%	18.5%
Digestive organs	18.7%	25.4%
Breast	2.2%	3.8%
Lung	2.2%	4.6%
Other	5.8%	7.7%
Karnovsky Status (>90%)	93/134 (69.4%)	87/ 130 (66.9%)

(Table prepared by the reviewer from Tables 4, 6 & 7 from sponsor's Vol. 5, pp. 10-29.)

In addition, 10 (7.2%) of the granisetron-treated group and 7(5.6%) of the placebo group had prostate cancer. Lymphoma and digestive system cancers were next most frequent at @ ± 20%, breast and lung cancers were studied less often and location for all other cancers ranged between about 6 and 8%.

Reviewer's Comment: This high inclusion of specifically male forms of cancer helps explain why the majority of patients in this study were males by a ratio of 1.9:1.

(e) **Clinical Response** (according to the sponsor)

1-Emesis control

An analysis of time to first episode of emesis is given in Table 7. The results show that the findings for this endpoint are similar between the ITT and PDA-defined groups.

Table 7

Time to First Episode of Emesis-ITT-Defined Analysis(ITT) Versus Protocol-Defined Analysis (PDA)

Median Time (Days)- ITT				
Granisetron (n=134)	Placebo (n=126)***	Hazard (Risk) Rate ****	p=Value for Relative Risk	95% Confidence Interval for Relative Risk Ratio Granisetron vs Placebo
35	9	1.89**	<0.001	(1.33, 2.67)
Median Time (Days)* PDA				
Granisetron (n=90)	Placebo (n=96)			
>28*	6	2.07**	0.001	(1.35, 3.17)

*Unable to compute median time to event because too few patients had emesis. Range data for all groups are not available. (** Indicates that the chance of emesis occurring in the untreated group is about double that for the treated group) (*** Four patients in the original 130 of this group were counted as "missing" for various reasons, including not receiving study medication.) (****Based on the Cox Proportional Hazard Regression Model)(Table modified from sponsor's Tables 13 and 14 in Vol. 4, pp. 63-64).

A gender-specific analysis of the time to first episode of emesis is shown in Table 8.

Table 8

Gender-specific Time to First Episode of Emesis-All Patients in the ITT Population Versus All Patients in the Protocol Defined Analysis (PDA)

Median Time (Days)-ITT		Median Time (Days)-PDA	
Granisetron	Placebo	Granisetron	Placebo
Males			
n=87	n=82	n=61	n=58
>28*	14.0	>28*	9.0
Females			
n=47	n=44	n=35	n=32
35.0	2.5	23.0	4.0

(* Unable to calculate median time to event because too few patients had emesis
(Modified from sponsors tables 13 and 14 in Vol 4, pp 63-64)

Despite the fact that the numbers are too small to arrive at significance, both the ITT and PDA analysis methods observe a tendency toward earlier times to first episode of emesis in females in the placebo-treated groups.