CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020623

ADMINISTRATIVE DOCUMENTS

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

DATE: February 6, 1997

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Approvable Recommendation for Anzemet (dolasetron mesylate) Injection and Tablets

TO: NDA 20-624 and NDA 20-623

Hoechst Marion Roussel has submitted two NDAs for dolasetron mesylate. NDA 20-623 is for a tablet formulation. That application is for prevention of cancer chemotherapy induced nausea and vomiting (CCNV) and prevention of post-operative nausea and vomiting (PONV). While there is no question about the efficacy of the drug, concerns were raised about cardiovascular risk because of the dose related effects of the drug on cardiac conduction. I concluded that for the CCNV indication, for the 200 mg dose more clinical safety data were needed. For the 100 mg dose recommended for PONV sufficient safety data was available to support approval of the drug at that dose. My memoranda of August 16, 1996 and September 20, 1996 provide the reasoning for those recommendations.

NDA 20-624 is for an injection formulation and in addition to the CCNV and PONV indications in common with the tablet NDA, an additional claim is requested i.e. treatment of post-operative nausea and vomiting (TO PONV). The medical and statistical reviews evaluate in detail the studies in support of each claim for the injection formulation.

The data in support of the treatment indication come from two clinical studies (MCPR044 and 73147-3-S-084). These two randomized double-blind placebo controlled multi-center studies evaluated doses of 12.5 to 100 mg of active drug versus placebo. The results (as per our statistician's report) were

Protocol MCPR0044
Complete Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo
placebo	13/121(11%)	
Dolasetron 12.5	46/130(35%)	<0.001*
Dolasetron 25	33/119(28%)	0.0007*
Dolasetron 50	36/124(29%)	0.0003*
Dolasetron 100	37/126(29%)	0.0005*

P-values were calculate from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose, gender and investigator as explanatory variables.
* significant at 0.05 level when controlling for 4 multiple comparisons to placebo using Dunnett's procedure.
Copied from Table 8-76, S8-v1.49-p133.

Protocol 73147-2-S-084
Complete Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo
placebo	8/71 (11%)	
Dolasetron 12.5	16/66 (24%)	0.0428
Dolasetron 25	18/65 (28%)	0.0094*
Dolasetron 50	25/67 (37%)	0.0005*
Dolasetron 100	17/68 (25%)	0.0388

p=0.0114 for test for linear trend.
P-values were calculate from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.
* significant at 0.05 level when controlling for 4 multiple comparisons to placebo using Dunnett's procedure.
Copied from Table 15, S8-V1.500-p107.

Our statistician notes for the 12.5 mg dose that:

"All dolasetron mesylate dose groups were significantly different from placebo at 0.5 level. However, when adjusted for multiple comparisons using Dunnett's procedure, only the 25 mg and 50 mg dose groups were significantly different from placebo."

Based on these results we would recommend a single 25 mg dose for TOPONV.

By protocol patients who entered did not have an initial preventive dose. Therefore we have no data in patients who failed the initial preventive dose.

As to safety, a single dose of 25 mg appears to be reasonably safe. Even if a preventive 25 mg dose were given, a second 25 mg dose should not exceed blood levels of the drug or metabolite that are reasonably safe. However, it seems reasonable to ask the sponsor for a study of the safety and efficacy of patients receiving a preventive dose of dolasetron mesylate followed by the treatment dose for those who have nausea and/or vomiting in spite of dolasetron prophylaxis. This has been requested.

As per the medical officer's report, the PONV dose for the injection formulation also appears to be 25 mg. This is considerably less than what we have suggested for the tablet (i.e. 100 mg). It is also reasonably safe and we would recommend that dose be approved for this indication.

For CCNV the proposed dose for the injection is 1.8 mg/kg. In light of the data from the injection NDA, a 100 mg dose for the tablet for CCNV might be reasonable and also approvable, although there is one study in which the 200 mg dose was significantly superior to the 100 mg dose. Since the major cardiovascular concerns are for doses of 200 mg and above, therefore a 100 mg dose may on balance be best.

New safety information also needs to be considered. A case of sudden death is described by the medical officer. Clearly the labeling must adequately inform the practitioner of the risks, and, based on assessment of the clinical experience with the

injection and tablet, a warning as well as a precaution is now proposed. With the information included in the draft labeling, I would recommend that Anzemet injection and tablets be approved.

/S/

Stephen Fredd, M.D.

cc:
NDA 20-624 & NDA 20-623
HFD-180
HFD-103/Dr. Botstein
HFD-180/Dr. Gallo-Torres
HFD-713/Dr. Huque
HFD-713/Dr. Fan
HFD-181/CSO/Ms. Johnson
HFD-180/Dr. Fredd: 1/30/97
f/t deg: 1/30/97/2/5/97/wpc:\wpfiles\fredd\m\nda20624.6sf

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

DATE: September 20, 1996

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 20-623

TO: Acting Director, Office of Drug Evaluation III, HFD-103

In response to your memorandum of September 19, 1996, while I am pleased that you agree with the recommendation that dolasetron be approved for PONV, I am puzzled by your statement that:

> It doesn't seem to me that a large study of cardiac adverse events is needed or is really feasible. We can discuss further what data might persuade that dolasetron be approved for CCVN.

I believe we need to know what the risk of QT prolongation is in the CCNV population at the 200 mg dose. If we not approve the CCNV indication at this time, we need to tell the sponsor what they must do to make the indication approvable. Our response to that would be for the sponsor to provide a larger and more representative safety database to assess the risk to CCNV patients given a 200 mg dose.

I do not agree that we will learn more about the real risk by further evaluations of the QT data. That seems clear and has already been reviewed by prominent cardiologists. The effect on prolongation of the QT appears to be due to QRS lengthening, not JT lengthening as noted in the Dr. Pradhan's biopharmaceutics review as follows:

> Changes in JT interval were, at most, marginally related to plasma concentrations of DMA and confounded by intrasubject variability in the measurements. The same was true for changes in heart rate. The relationship of plasma concentrations of DMA to increases in QTc interval and a significant linear relationship between plasma concentrations of DMA and increases in QRS duration, taken together, support the conclusion that increases in QTc interval after dolasetron mesylate are the result of increases in QRS duration (depolarization) and may not be

because of any prolongation of JT interval (repolarization) or heart rate.

As you know, prolongation of JT is associated with Torsades, while QRS prolongation can result in heart block. Clearly either is of concern, and further clinical safety experience can be obtained to estimate any real risk of the 200 mg dose in the CCNV population.

As to dose reduction, I do not think that is necessary for PONV and a 100 mg single dose.

We have the following statement in the proposed labeling:

PRECAUTIONS

Administration of dolasetron mesylate to patients and volunteers has resulted in predictable, reversible changes in electrocardiographic intervals; specifically, increases in the PR interval, QRS duration and Qt_c interval have been observed. When administering dolasetron to patients with pre-existing cardiac disease, conduction abnormalities, or drugs that affect conduction, particular care should be taken such as electrocardiographic monitoring.

That seems to us appropriate for the proposed PONV approvable action. Clearly were we to recommend approval of a 200 mg dose for CCNV we might suggest more depending on the clinical data.

In considering your memorandum, I believe we think that what has been done thus far in review, analysis, labeling is sufficient to support the action on PONV. You have agreed with that action. For CCNV at a 200 mg dose we also agree that it should not be

approved at this time. The action letter to the sponsor to that effect would help moving the knowledge base forward, therefore the action letter and supporting data are returned to you with the package for your reconsideration.

/S/

Stephen Fredd, M.D.

cc:
NDA 20-623
HFD-180
HFD-181/CSO/Ms. Johnson
HFD-180/Dr. Gallo-Torres
HFD-180/Dr. Fredd: 9/20/96
f/t deg: 9/20/96/wpc:\wpfiles\fredd\m\nda20623.3sf

Office of Drug Evaluation III
Room 13B45 Parklawn

ODE III

phone 301-827-3144
fax 301-480-3761

DATE: 12/12/96

TO: Director
Division of Gastro-intestinal and Coagulation Drug Products

FROM: Acting Director
Office of Drug Evaluation III

SUBJECT: NDA 20,623. dolasetron [Anzemet],
Hoechst Marion Roussel.

This memo confirms my oral request to you to obtain a consultation from the Division of Cardiorenal Drug Products on the cardiovascular effects of dolasetron.

The sponsor has made a comprehensive submission in response to questions about effects on QT etc. This submission, made in response to my memo to you on September 19, 1996, has not been reviewed in your division and needs review.

Dolasetron prolongs the Q-T interval and therefore carries some degree of risk of Torsades de pointes and other ventricular tachy-arrhythmia's. Marketed drugs in this class are not known to prolong the QT.

We would like a full consultation on the characterization of dolasetron's cardiac effects, the sufficiency of the data, and on the level of clinical concern raised. This includes consideration of the benefit/risk ratio for the drug.

Please inquire whether further clinical or metabolic study is recommended, and if so, what kind. Do they recommend taking this drug to the Cardiorenal Advisory Committee?

Although we have tentatively concluded that the drug is approvable for post-op nausea and vomiting at a dose of 100 mg, please ask our cardiac consultants for their recommendations on this.

Please also ask for a labeling review and recommendations for label language.

Our consultants may well want to meet with people in your division to discuss the consultation and the data. I encourage you to facilitate whatever meetings or discussion are asked for.

Although a goal date for this drug approaches, resolving the safety issues for this drug is more important than issuing an action letter this month.

Thank you.

/S/

Paula Botstein M.D.

cc:
NDA
HFD 180/MO
HFD 180/CSO
HFD 180/biopharm
HFD 103/Collier
HFD 103/dolasetron
HFD 103/sig
HFD 103/chron

Office of Drug Evaluation III
Room 13B45 Parklawn

CDE III

phone 301-827-3144
fax 301-480-3761

DATE: September 19, 1996

TO: Director
Division of Gastro-intestinal and Coagulation Drug Products

FROM: Acting Director
Office of Drug Evaluation III

SUBJECT: NDA 20,623. dolasetron tablets [Anzemet, Hoechst Marion Roussel]

I agree that dolasetron po should be indicated for post-operative nausea and vomiting [PONV], with labeling changes, and not for nausea and vomiting from cancer chemotherapy [CCNV], because of the differences in dose and dose-related risk of cardiac events. It doesn't seem to me that a large study of cardiac adverse events is needed or is really feasible. We can discuss further what data might persuade that dolasetron be approved for CCVN.

The QTc data from the 2 trials of CCNV is useful because it shows that QTc is prolonged after one dose at the dose recommended for effectiveness. After a dose of 200 mg orally, QTc is prolonged at the single time point selected for EKG, on average, in a group of patients without identified risk factors. These trials also provide QTc data at a clear time point in awake patients not full of anesthetic drugs.

One study in CCNV provides strong evidence of the QTc prolongation by dolasetron and the other provides consistent but not statistically significant data. Experience, with terfenadine and other drugs that prolong QTc and with the hereditary disorder of prolonged QTc, shows that if QTc is sufficiently prolonged Torsades de pointes and other tachyarrythmias follow inexorably at least in rare patients. The degree of QTc prolongation necessary in an individual patient for Torsades is not known, although a frequently cited range of major risk is above 500 millisec. Patients with prolonged QTc less than 500

millisec but more than about 440 have increased risk of Torsades. QTc can rarely be measured continuously, and an instant value will not reflect the fact that greater prolongation may occur at other time points after dosing. In addition, some patients will have risk factors which make for synergy in QTc prolongation. These patients are typically not studied in large numbers in clinical trials and their frequency and risk are not quantitated.

Time of risk is less for a drug used episodically than for one used chronically, and dolasetron is used episodically.

For CCNV, effectiveness occurs in a high percentage of patients at a dose of 200 mg, at a rate comparable to that from ondansetron in one comparative study.

Dolasetron used for PONV might have a lower risk of consequences from increased QTc while patients are under anesthesia and monitored in an operating room or recovery room.
Dolasetron is used for PONV at a dose lower than for N & V from chemotherapy. Lower doses , of course, carry risk of QTc prolongation in some people, although not much or in as many.

The effects of dolasetron on QTc interval need to be better characterized before we can determine what cautions and information are needed in labeling .

Information useful for assessing the effect of dolasetron on the QTc.
Writing labeling that provides for safe use of dolasetron requires additional evaluation or locating of information and data, such as that iterated below. Although some of this information is certainly in reviews of individual studies, it needs pulling together. Other parts may well be in the NDA, or known by the reviewers, or can be requested of the sponsor. The issue is the characterization of the available data and not of obtaining new data.

List of studies in which QTc was measured

These studies listed by dose
by indication

Was the timing of EKGs appropriate for detecting the effect on QTc?
---Time of EKGs after drug administration
--Time of expected peak blood level

Were EKGs of appropriate frequency to characterize the time course of the effect on QTc ?

Was the methodology for reading EKGs standardized, specified in advance, and adequate in the studies?

What is the magnitude of the effect on QTc ?
--Mean changes
--Changes in those patients with the most change
--Changes in those patients with the longest QTc's at baseline
--Changes in those patients with the longest QTc"s after dosing
--Compared with the magnitude from other drugs known to increase QTc

Effects on QTc
by dose
by dose/kg of body weight
compared with control
by gender
by age

Rate of dizziness or other possibly related symptoms to dose

Reports of prolonged QTc in patients other than those in the above studies
--tallied
--including child overdosed with 6mg/kg

Metabolism and effect of P450 drugs

Dolasetron is evidently converted almost completely to DM. Is D or DM the species responsible for the increase in QT?

DM is metabolized by the cytochrome P450 enzymes CYP IID6 and IIIA, among other enzymes not noted. What drugs are known to affect these enzymes and would be expected to cause increased levels of D or DM?

Results of studies with cimetidine [incr AUC of DM] and with rifampin [decrease in AUC of DM], are consistent with these drugs changing the metabolism of dolasetron. Are these drugs known to affect the enzymes CYP IID6 and CYP IIIA ?

QTc and plasma concentration
The biopharm review mentions the data on the relationship between QTc and increasing concentrations [presumably in plasma]. [e.g.pII, para 3, line 1]. Where is this data and what do you think of it?

Renal function
Should the dose should be decreased in patients with marked renal impairment? I think so, but let 's discuss.

I don't find the data on QT prolongation in patients with impaired renal function. This data is mentioned several places in the biopharm review [e.g., p II, para 3].

Hepatic function
Should the dose should be decreased in patients with hepatic impairment. in light of QTc prolongation? I think so; let's discuss.

Elderly
Are the differences in AUC [incr], Cl [decreased], t 1/2 [sl decr] meaningful?

Misc.
So far as the prognostic significance and magnitude of the other effects on EKG discussed in various separate places in the medical review, I do not know and have not attempted to pull together the data. I recommend consultation with our cardiology experts.

Biopharm rev. recommends decreasing dose of concomitant atenolol. What is the data and what do you think of it?

Needed before approval
Statistics review and perhaps consultative cardiology review of the EKG data.

Labeling

The labeling of dolasetron needs to discuss its cardiac adverse properties prominently and straightforwardly. Recommendations follow. The vigor of the cautionary language should depend partly on whether commonly used drugs are likely to be synergistic with dolasetron in prolonging the QTc.

1]. Clear language that dolasetron prolongs the QTc interval.
2].The potential consequences of prolonged QTc [Torsades de pointes and other ventricular tachyarrythmias, which can be serious and fatal; syncope]. It might be stated that these events have not been reported so far with dolasetron but are the expected consequence of drugs that prolong QTc.
3]. Description of the QTc prolongation --doses, extent and magnitude of increase, percent of patients with increase, type of patients, etc. This can be brief.
4].Cautions about using the drug in patients with already prolonged QT or at risk of having prolonged QTc even without dolasetron [hypokalemia, hypomagnesemia, taking drugs likely to increase levels of dolasetron or its metabolites]
6. Not using certain drugs concomitantly [if appropriate]
7. The dose should not be increased.
8]. ? lower dose or caution for patients with marked hepatic or renal insufficiency.
9]. Other relevant information from above.

We are close.

/S/

Paula Botstein M.D.

cc:
NDA
HFD 180/MO
HFD 180/CSO
HFD 103/Collier
HFD 103/dolasetron file
HFD 103/sig file
HFD 103/chron

Johnson

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

DATE: August 16, 1996

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Recommendations for Dolasetron Tablets.

TO: NDA 20-623

Hoechst Marion Roussel submitted an NDA for Dolasetron tablets for prevention of 1) chemotherapy induced nausea and vomiting and 2) post-operative nausea and vomiting (PONV). The sponsor recommends a 200 mg single oral dose for chemotherapy induced nausea and vomiting, and a 50 mg single oral dose for PONV. As will be discussed in this memorandum, I recommend approval only for the PONV indication at this time.

Dolasetron is a $5HT_3$ receptor antagonist similar to Ondansetron and Granisetron, drugs already approved for these indications. No claim is made for superior efficacy for Dolasetron. It would provide another choice for patients undergoing these procedures. As such, however, Dolasetron should not be less safe than the already approved agents. Since all of the $5HT_3$ receptor antagonists can at some dose involve other receptors, such as $5HT_4$ receptors, we have been concerned for all drugs in this class that the dose be carefully chosen so that the possibility of cardiac adverse events are minimized. Therefore there must be careful consideration of the Dolasetron dose and special populations such as cardiac patients.

For the chemotherapy indication, studies 43, 48 and 87 evaluated single oral doses from 25 mg to 200 mg. Study 87 suggests that 200 mg is the most effective dose as evidenced by the following table of complete response from our statistician's report.

Protocol 73147-2-S-087
Complete Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	p*-value vs Onda	p*-value vs 25 mg	p*-value vs 50 mg	P*-value vs 100 mg
Onda	60/83 (72%)				
Dola 25	36/80 (45%)	0.0003			
Dola 50	39/79 (49%)	0.0011	0.6584		
Dola 100	46/76 (61%)	0.0640	0.0638	0.1613	
Dola 200	61/80 (76%)	0.5787	<0.0001	0.0002	0.0184

p<0.0001 for linear trend in dolasetron mesylate dose.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with treatment, stratum, and investigator as explanatory

Also the 200 mg Dolasetron dose has efficacy similar to Ondansetron.

Studies 43 and 48 do not demonstrate statistical superiority of the 200 mg dose to the 100 mg dose, but support efficacy for either. There has been no study in high dose cisplatin regimens to determine whether 100 mg or 200 mg should be used. Based on study 87, I would select a 200 mg dose, provided it was shown to be safe.

Data to support the safety of the proposed 200 mg dose has been provided, and there is a major concern. The sponsor does not dispute the fact that Dolasetron has an effect on cardiac conduction. It lengthens the PR and QT intervals, most markedly at the 200 mg dose. These changes are reversible. To determine what the risk of this finding is to patients, we need to have sufficient exposure of the target population to see if serious cardiovascular events occur. The sponsor provides opinion from two cardiologists and 2 oncologists on this matter which is summarized as follows:

"Administration of dolasetron mesylate to patients and volunteers has resulted in predictable, reversible changes in electrocardiographic intervals; specifically, increases in the PR interval, QRS duration and QT_c interval have been observed. The significance of these changes is addressed by cardiologist

consultants Craig M. Pratt, MD and Claude R. Benedict, MD,DPhil in attached expert opinions (Pratt 1995b, S8-VI.687-P407 and Benedict 1995a,S8-VI.683-P126), as well as clinical investigators/practicing oncologists Mark G. Kris, MD, et al, and David Gandara, MD, et al in attached publications (Kris 1994, S8-VI.686-P269 and Gandara 1994, S8-VI.685-P169). While these dose-related changes are observed on 12-lead ECG recordings, they are not associated with cardiac events of clinical consequence in the opinion of these consultants/investigators and the Sponsor.

Dr. Pratt, in his Analysis of the Cardiovascular Safety of Dolasetron Mesylate letter of August,1995, acknowledges the electrocardiographic changes associated with dolasetron mesylate, which were summarized by Dr. Benedict. Given these changes, he asserts that the important clinical challenge is to answer the question "Are there any adverse cardiovascular clinical consequences to the use of dolasetron mesylate for patients either postoperatively or following chemotherapy?" His answer is no, with no episode of Torsades des pointes observed, no cardiac arrests or ventricular fibrillation attributed to dolasetron mesylate, and no episode of severe bradycardia or high degree heart block requiring either temporary and/or permanent ventricular pacing following dolasetron mesylate treatment. Additionally, the incidence of bundle branch block was similar following dolasetron mesylate or comparative agents. He concludes that he finds no evidence in the entire safety database containing over 7000 dolasetron mesylate individuals that there are cardiac events of clinical consequence attributable to dolasetron mesylate.

Dr. Benedict's Cardiovascular Expert Report for Dolasetron Mesylate dated April 20, 1995, quantifies the magnitude and predictability of ECG interval changes at the time of peak plasma concentrations of MDL 74,156 (the active metabolite of dolasetron mesylate). He notes that in most instances, treatment-emergent prolongations of PR, QRS, and QT_c following dolasetron mesylate or ondansetron administration would not have been detected except by computerized 12 lead ECG recordings. He indicates that prolongation of the QT interval (classically measured as QT_c) is the change associated in clinicians' minds with the likelihood of developing Torsades des pointes and resulting sudden death. This has not been observed in clinical practice or investigational studies with either ondansetron or dolasetron mesylate. He concludes that the overall cardiovascular risk associated with dolasetron mesylate treatment is small and dolasetron mesylate

appears to be as safe ondansetron at recommended doses.

The occurrence of predictable, dose dependent increases in electrocardiographic intervals, and lack of associated clinically significant cardiovascular events in cancer patients is also reported by Drs. Kris, et al, and Gandara, et al. They conclude that these electrocardiographic changes do not appear to be clinically important and should not limit the use of dolasetron mesylate or other 5-HT_3 antagonist."

The sponsor provides a summary table of the approximately 7000 patient safety database as follows:

Table 2-85. Adverse Events or Clinical Outcomes During the First 24 hours* Following Chemotherapy and PONV Combined - IV and Oral

	CCNV			CCNV		PONV Prevention			PONV Treatment		PONV Prevention		Total Patients			
Adverse Event Preferred Term	IV Meto	IV Ondan /Gran	IV Dol	Oral Ondan	Oral Dol	IV Plac	IV Ondan	IV Dol	IV Plac	IV Dol	Oral Plac	Oral Dol	Plac	Meto	Ondan /Gran	Dol
n (%)	193	356	2265	83	943	547	132	1785	192	765	231	936	970	193	571	6694
Deaths†			2 (.09)													2 (.03)
Torsades des pointes‡																
Cardiac Arrest																
Severe Bradycardia, Heart Block, or Bundle Branch Block requiring temporary or permanent pacemaker‡																
Ventricular Fibrillation																
Syncope		2 (.56)	2 (.09)			1 (.18)		3 (.17)		1 (.13)			1 (.10)		2 (.35)	6 (.09)
All Bundle Branch Block		2 (.56)	5 (.22)		1 (.11)		1 (.76)			1 (.13)		3 (.32)			3 (.53)	10 (.15)
LBBB with History			2§ (.09)													2 (.03)
LBBB Indeterminate or New		1 (.28)			1 (.11)		1 (.76)					1 (.11)			2 (.35)	2 (.03)
LBBB Rate Dependent																
RBBB with History																
RBBB Indeterminate or New		1 (.28)	2 (.09)							1 (.13)		1 (.11)			1 (.18)	4 (.06)

For oral Dolasetron there are 1879 exposures, approximately half in the PONV group. Since dose ranges of 25 mg to 200 mg were evaluated in both indications (note that the sponsor selected a 50 mg dose for the PONV indication), perhaps 470 patients have been exposed to a 200 mg oral dose in controlled studies, half for the cancer chemotherapy indication. There is one case of RBBB occurring 115 minutes after taking a 200 mg dose in one PONV patient who was also on veraparmil. The bundle branch block resolved in 24 hours.

It should be noted that the IV dose of Dolasetron studied was 1.8 mg/kg which would not be sufficient to assess risk of a 200 mg tablet. As noted in the biopharmaceutics review, Dolasetron must be metabolized into the active form called DMA by the reviewer. A linear relationship between plasma concentrations of DMA and prolongation of the QRS was demonstrated. The PK of Dolasetron given orally and IV over a 50 to 200 mg dose range was studied, and a comparison of the PK of an oral versus IV 200 mg Dolesetron dose was shown to be similar (study MCPR0035).

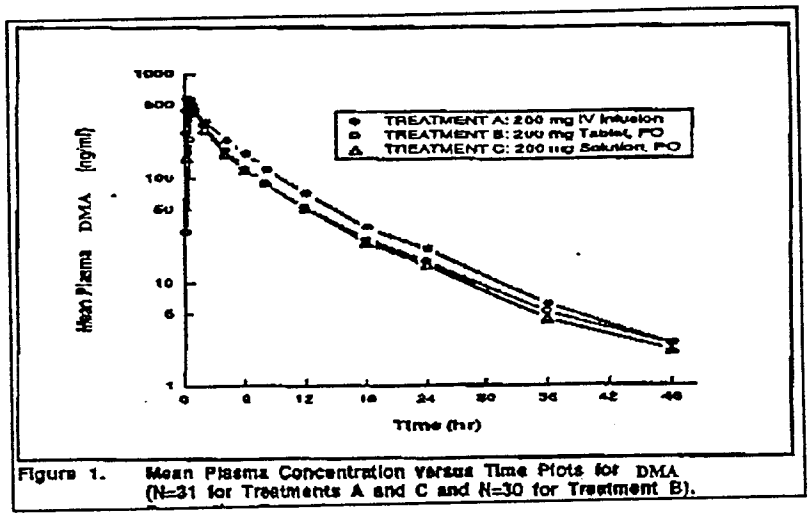

Figure 1. Mean Plasma Concentration versus Time Plots for DMA (N=31 for Treatments A and C and N=30 for Treatment B).

Therefore a 100 mg IV Dolasetron dose would not be equivalent to a 200 mg oral dose re cardiovascular risk assessment.

Since we believe the safety database is sufficient to recommend approval of the PONV indication at a 100 mg dose, a comparison of the size of the available safety databases seems needed. For the 100 mg PONV indication the IV database plus the oral database including 100 mg and 200 mg seems applicable. This would provide approximately 2725 patients for safety assessment. Seeing no Torsades in that number of patients would give reassurance that a 0.1% incidence would not be missed with a probability of .95 as per the following.

Dr. Robert O'Neill (Biopharmaceutics Statistics for Drug Development, Marcel Dekker Inc., 1988, p543-602) provided a chart showing the sample sizes needed to observe at least one adverse event with varying probabilities of detection.

Table 11 Sample Sizes Needed to Observe with Probability P at Least One Adverse Event Whose True Rate is R in a Given Time Interval

Event rate R	P						
	.99	.95	.90	.80	.70	.60	.50
.001	4603	2994	2301	1609	1203	916	693
.005	919	598	459	321	240	183	138
.010	458	298	229	160	120	91	69
.050	90	58	45	31	23	18	14
.060	74	48	37	26	19	15	11
.070	63	41	32	22	17	13	10
.080	55	36	28	19	14	11	8
.090	49	32	24	17	13	10	7
.100	44	28	22	15	11	9	7
.150	28	18	14	10	7	6	4
.200	21	13	10	7	5	4	3
.250	16	10	8	6	4	3	2

Also, while the sponsor states that patients with cardiovascular risk factors were included in the total safety database, for chemotherapy studies 43 and 48 there were exclusions for arrhythmias and congestive failure.

While one could consider, as the medical officer has, approving a 100 mg dose, since study 87 shows that 200 mg is significantly better than the 100 mg dose, and would probably be used, even if not recommended, we cannot avoid the need for adequate safety data for the 200 mg dose in this patient population. I think we should have sufficient safety reassurance before approval of the 200 mg. Therefore I would request additional study of the 200 mg oral dose in chemotherapy patients with cardiovascular risk factors as well as in the setting of high dose cisplatin therapy.

For assurance equal to that available for the proposed dose of the PONV application, approximately 2500 more patients would need to be studied. We will need to consider with the sponsor what a reasonable additional number will be to provide adequate risk assessment in this patient population.

For the PONV indication the medical officer makes the case that 100 mg should be the dose rather than 50 mg. Complete response in study 95 as found in the medical officer's review was as follows:

Response by Dose (mg)/Therapeutic Gain (%) and p-value[a] for PL Comparison					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses/[p-values][b]					
I. Intent-to-Treat Analysis (n=373)										
PL [n=75]	25 [n=75]	50 [n=74]	100 [n=74]	200 [n=75]	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
22 (29.3%)	27 (36%)	30 (40.5%)	40 (54.1%)	37 (49.3%)						
	(6.7%) [N.S.]	(11.2%) [N.S.]	(24.8%) [0.0026]	(20.0%) [0.0139]	(4.5%) [N.S.]	(18.1%) [0.033]	(13.3%) [N.S.]	(13.6%) [N.S.]	(8.8%) [N.S.]	(-4.8%) [N.S.]
II. Efficacy Evaluable Analysis (n=344)										
[n=68]	[n=71]	[n=71]	[n=66]	[n=68]						
22 (32.4%)	27 (38%)	30 (42.3%)	36 (54.5%)	36 (52.9%)						
	(5.6%) [N.S.]	(9.9%) [N.S.]	(22.1%) [0.014]	(20.5%) [0.024]	(4.3%) [N.S.]	(16.5%) [N.S.][c]	(14.9%) [N.S.][d]	(12.2%) [N.S.]	(10.6%) [N.S.]	(-1.6%) [N.S.]

a,b) Obtained by Fisher's Exact Test. Calculated by Dr. M. Fan, FDA Biometrician
c) Borderline at 0.061
d) p-value=0.090.

For study 292:

Response by Dose (mg)/Therapeutic Gain and p-value[a] for PL Comparison					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses/[p-values[b]]					
I. Intent-To-Treat Analysis (n=789)										
PL [n=156]	25 [n=159]	50 [n=166]	100 [n=154]	200 [n=154]	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
55 (35.3%)	71 (44.7%)	95 (57.2%)	78 (50.6%)	73 (47.4%)						
	9.4% [N.S.]	21.9% [0.0001]	15.3% [0.0062]	12.1% [0.0181]	12.5% [0.0243]	5.9% [N.S.]	2.7% [N.S.]	-6.6% [N.S.]	-9.8% [N.S.]	-3.2% [N.S.]
II. Efficacy Evaluable Analysis (n=747)										
[n=149]	[n=153]	[n=157]	[n=143]	[n=145]						
53 (35.6%)	69 (45.1%)	91 (58.0%)	72 (50.3%)	68 (46.9%)						
	9.5% [N.S.]	22.4% [<0.001]	14.7% [0.013]	11.3% [N.S.[c]]	12.9% [0.031]	5.2% [N.S.]	1.8% [N.S.]	-7.7 [N.S.]	-11.1 [N.S.[d]]	-3.4 [N.S.]

a,b) Obtained by Fisher's exact test. Calculated by Dr. M. Fan, FDA Biometrician.
c) Borderline, at 0.058. d) Borderline at 0.065.

The 100 mg dose is effective in both studies, and there is no gain in using 200 mg.

Since 100 mg is the proposed dose, dose adjustment for special populations such as the renally impaired does not seem necessary. For a 200 mg dose, dose adjustment would be needed. Although only women were in these oral PONV studies, no gender difference in PK was found. Therefore, for this drug the indication can be a general one for adults with a notation in the clinical trials that males were not studied.

There is some information for the PONV pediatric population, but only in 11 subjects have been given the drug in the IV formulation orally. The PK of these pediatric patients ages 2-11 years, was contrasted to the adult population in the following chart from the biopharmaceutics report.

Parameters	Mean (%CV)			
	Oral		IV	
	Pediatric Surgery Patients (2 to 12 yr, N=11)	Adult Healthy Volunteers (20 to 43 years, N=16)	Pediatric Surgery Patients (2 to 11 yr, N=18)	Adult Healthy Volunteers (19 to 40 years, N=24)
Dose	1.2 mg/kg	1.3 mg/kg	1.2 mg/kg	1.27 mg/kg
AUC_{∞} (ng.h/ml)	933 (61)	1181 (39)	1356.0 (42)	1797 (28)
Cmax (ng/ml)	159 (32)	225 (24)	254.6 (22)	320.0 (25)
tmax (h)	1.39 (70)	0.70 (30)	0.63 (57)	0.62 (64)
CLapp,po (ml/min/kg)	20.77 (49)	15.5 (35)	-	-
CLapp (ml/min/kg)	-	-	13.13 (47)	9.39 (28)
Vapp (L/kg)	-	-	5.17 (43)	5.77 (25)
t1/2 (h)	5.89 (24)	7.47 (21)	4.77 (23)	7.32 (24)

There appear to be differences between the drug given IV or orally in these pediatric patients, as well as differences compared to adults. One pediatric patient given 6 mg/kg in error developed transient QT prolongation. While the sponsor recommends a dose of 1.2 mg/kg for the pediatric population, I do not think enough dose ranging has been done to suggest an effective and safe dose for pediatrics. A phase IV commitment to evaluate this question should be obtained.

A letter with draft labeling to make Dolasetron tablets approvable to prevent postoperative nausea and vomiting in adults at a single 100 mg dose will be drafted.

/S/

Stephen Fredd, M.D.

cc:
NDA 20-623
HFD-180
HFD-103/Dr. Botstein
HFD-180/Dr. Gallo-Torres
HFD-713/Dr. Huque
HFD-870/Dr. Pradhan
HFD-181/CSO/Ms. Johnson
HFD-180/Dr. Fredd: 8/16/96
f/t by deg:8/16/96/8/19/96wpc:\wpfiles\fredd\m\nda20623.1sf

13/14. Patent Information / Certification

PATENT NUMBER: United States Patent No. 4,906,755

EXPIRATION DATE: March 6, 2007

PATENT OWNER: Merrell Dow Pharmaceuticals Inc.
2110 E. Galbraith Road
Cincinnati, OH 45215-6300,
a wholly-owned subsidiary of
Hoechst Marion Roussel, Inc.
Marion Park Drive
Kansas City, MO 64137-1405

TYPE OF PATENT: Drug Substance Patent

The undersigned also declares that United States Patent No. 4,906,755 covers dolasetron mesylate, the drug substance of the product for which NDA 20-623 is being submitted for approval, September 28, 1995, as well as any formulation, composition or method of use which employs said drug substance.

This declaration is submitted herewith. Please list the No. 4,906,755 patent in the Orange Book Publication upon approval of the NDA.

Submitted by: Elaine Waller

Elaine Waller
Vice President,
U.S. Regulatory Affairs

copies

EXCLUSIVITY SUMMARY for NDA # 20-623 SUPPL #_____

Trade Name Anzemet Tablets **Generic Name** dolasetron mesylate
Applicant Name Hoechst Marion Roussel **HFD-** 180

Approval Date 9/11/97

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 /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

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

   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:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

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 /___/ NO /_X_/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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 /___/ 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 /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

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 /___/

(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 # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/
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 /___/
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 # _____

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 /___/ 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 /___/

If yes, explain: _____

_____

_____

_____

/S/ 9/10/97

Signature Date

Title: Supervisor, Project Management Staff

/S/ 9-10-97

Signature of Division Director Date

Acting

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

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-623 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

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

Applicant Hoechst Marion Roussel Therapeutic Class 15

Indication(s) previously approved —

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application prevention of chemo-induced emesis prevention of post operative N & Vomiting (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.
firm will provide a protocol following approval

___ 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.

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

/S/ — 9/5/97

Signature of Preparer and Title — 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

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-623 Trade (generic) names Anzemet (dolasetron) Tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

✓ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
✓ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. 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 do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

/S/

Signature of Preparer

8/28/96

Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

/S/

8/29/96

Debarment Certification

Hoechst Marion Roussel, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debared under Section 306(a) or (b) in connection with this application.

Elaine Waller

Elaine Waller, PharmD
Vice President, US Regulatory Affairs

9.28.95
Date

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 27, 1997
SEP - 2 1997

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader HFD-110 Division of Cardio-Renal Drug Products

SUBJECT: Dolasetron Mesylate (NDA 20-623) and Cardiovascular Events.

TO: Lilia Talarico, M.D. Acting Director, Division of Gastro-intestinal an Coagulation Drug Products, HFD 180

This review is a response to your consultation request dated 25 June 1997. The information that was reviewed was the 5 volumes submitted by Hoechst Marion Roussel on 9 June 1997, the single volume submitted on 29 July 1997 and Volume 1.3 of the original NDA. The information submitted by Hoechst Marion Roussel on 29 July 1997 was in response to a request for additional information.

The specific questions that you asked me and there answers follow. I've put together a listing of possible regulatory actions at the end of this review.

Answers to Specific Questions:

1. What is the total number of patients treated with 200 mg orally?

The sponsor is better able to screen the data base to answer this question. Based, however, on the information submitted, there were 238 subjects treated with 200 mg orally for cancer chemotherapy nausea and vomiting; 233 subjects treated for post-operative nausea and vomiting and 242 normals. There were an additional 36 normal subjects who were treated with doses higher than 200 mg. There were, therefore, a total of 739 patients/normals who were treated with oral doses of $\geq$ 200 mg of Dolasetron (see Table 1 of my review dated 15 January 1997).

2. Of this total, how many had significant cardiovascular conditions, especially those that may pre-dispose the patient to QT/QTc prolongations, A-V block, etc.?

Among these patients the sponsor tabulated a total of 134 subjects that were deemed to have underlying cardiovascular conditions. Nineteen subjects had objective evidence of coronary artery disease such as previous myocardial infarction, previous angioplasty or angina. An additional 53 subjects had the cardiovascular

disease was listed solely as arterial hypertension. The residual 62 patients had conditions listed as atrial arrhythmias, peripheral vascular disease, coronary artery disease, as well as valvular disease that were not further described. Subjects could have any one or combination of these conditions.

So my estimate is that at the minimum 19 subjects had cardiovascular disease proven. An additional 62 subjects may or may not have had cardiovascular disease and the 53 subjects with arterial hypertension are unlikely to have major cardiovascular disease.

3. Were there dolasetron-induced prolongations of the ECG parameters in these subgroup of patients? If so, in you judgment, are these clinically meaningful effects?

Dolasetron, at 200 mg single dose, in considering a population consisting of both normals and those with sponsor defined cardiovascular diseases, caused increases in PR, QRS and QTc intervals. The sponsor also tabulated the JTc values below. There was a statistically significant trend to increase in JTc in one study (#43; $p < 0.005$), marginally significant in one study (# 292 ; P=0.09) and not significant in one study (#048; p=0.14).

Table 1. Change in JTc ($msec^{-1/2}$) at approximately 1-2 hours Post Dose in the Composite in the Prevention of Post-Operative Nausea and Vomiting and Cancer Chemotherapy Nausea and Vomiting :

Study #	Placebo	25 mg	50 mg	100 mg	200 mg
# 43	_____	**7.6**	**3.7**	**3.5**	**16.6**
# 48	_____	6.3	5.4	9.2	9.7
# 87*	_____	_____	_____	_____	_____
# 95	No	Data	Available	At Any	Time
# 292	22	24	26	26	28

* Study had no PR measurements except at 24 hours

Among the 19 subjects that appeared to have distinct evidence of coronary artery disease, there were 16 subjects who had both baseline and on therapy ECGs. The change from baseline for these subjects for their ECG parameters is shown later as Table 9.

4. Of the total, the number of patients taking concomitant medications that may prolong ECG parameters?

I do not have adequate breakdown of the concomitant medications. One of the subjects who died pt # 73147-3-S-093,093-110/A either was on, or was previously treated with flecainide.

5. Of the total, the number of patients taking anthracyclines?

I do not have a breakdown of those patients who were treated with anthracyclines. I do remember prior to the last meeting that the sponsor submitted a relatively few subjects who were treated with anthracyclines. Few had substantial

cumulative doses and the data was not sufficient to draw any conclusion. One of those who died pt 73147-#-S-082,082-043A, had cumulative exposure of > 320 mg of doxorubicin.

6. What is you overall assessment of the exposure and safety of the 200 mg dose?

The number of patients exposure to dolasetron at 200 mg is not trivial but the duration of exposure was generally limited to single doses. In addition, few of these patients had convincing evidence of cardiovascular disease at baseline. It is furthermore, impossible to determine the number of subjects who conformed to the CAST I and CAST II population i.e. Those s/p myocardial infarction with decreased ejection fraction and ventricular ectopy.

There were no deaths in the 200 mg oral dose group within 48 hours of treatment. The power of this data base, however, is modest and a risk equivalent to that seen in CAST I or CAST II cannot be ruled out. Based on the lack of continuous electrocardiographic monitoring some rhythm disturbances may have been missed.

Background:

Dolasetron is a anti-emetic with proposed indications in the prophylaxis of both post-operative nausea and vomiting as well as in chemotherapy-induced nausea and vomiting. This drug would be the third member of the 5-HT_3 blocking drugs approved for these indication. Dolasetron differs from the other two members of this class, Ondansetron Hydrochloride (Zofran®) and Granisetron Hydrochloride (Kytril®), in that Dolasetron, both in animals and humans, appears to be a sodium channel blocker. Dolasetron (more accurately its active metabolites) decreases Vmax (dV/dt) in guinea pig papillary muscle. When Dolasetron was administered to humans the PR, QRS and QT intervals of the ECGs were prolonged, consistant with its sodium channel blocking properties. Dolasetron also appears to prolong repolarization and therefore may also be a potassium channel blocker

Sodium channel blockers are most often used as anti-arrhythmic drugs and are further subclassified as Ia, Ib or Ic based on the time constants needed for functional recovery of these channels. In guinea pig, Dolasetron appears to act as a Ic sodium channel blocker.

In the Cardiac Arrhythmia Suppression Study (CAST[1]), when flecainide or encainide, both Class Ic sodium channel blockers, were administered to patients who survived a myocardial infarction and who had asymptomatic ventricular ectopy, the composite of mortality and resuscitated sudden deaths were markedly increased relative to placebo. These drugs are also labeled as increasing the incidence

[1]The Cardiac Arrhythmia Suppression (CAST) Investigators."Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression After Myocardial Infarction" N Eng. J. Med 1989:321: 406-12.

of a wide range of cardiac rhythm disturbances.

By analogy with flecainide and encainide, all antiarrhythmic drugs carry a WARNING that mortality may be adversely affected and that potentially life-threatening rhythm disturbances may be increased.

The labeling for flecainide implies that there is a relationship between trough serum concentration and cardiac adverse events.

This WARNING, included in all Class I anti-arrhythmics (as well as most anti-arrhythmics of other classes) reads as follows. The black-box WARNING for Procainamide (Procanbid) is used as a prototype.

Under WARNINGS:

Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term multi-centered, randomized, double-blind study in patients with asymptomatic, non-life threatening ventricular arrhythmias who had a myocardial infarction more than 6 days but less than 2 years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in the study was 10 months.

The applicability of the CAST results to other populations (eg those without recent myocardial infarction) is uncertain. Considering the known pro-arrhythmic properties of procainamide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life threatening arrhythmias, the use of Procanbid as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

This black-box warning is included in procainamide's labeling despite the lack of data that mortality with procainaimde is increased and despite the difference in sodium channel binding characteristics of procainamide, a Class Ia antiarrhythmic, relative to flecainide, a Class Ic antiarrhythmic.

The extent to which the above WARNING or some PRECAUTIONARY statement should be included within the labeling of Dolasetron, by analogy with other Class I sodium channel blocking drugs is the pivotal decision. In contrast to anti-arrhythmics, the target population for Dolasestron does not generally consist of patients with underlying cardiac disease, are not status/post-myocardial infarction and do not have ventricular ectopy and a decreased ejection fraction.

A second difference between Dolasetron treatment and the drugs used in CAST I is that Dolasetron is administered discontinuously whereas the drugs to treat arrhythmias are used continuously. There is, however, data that even over

short periods of time, Moricizine, a Class Ic drug used in the CAST II[2] study was associated with a substantial increase in mortality, particularly in the first two weeks of treatment.

CAST II was an outgrowth of, but differed in several way from, the CAST I study. CAST II enrolled patients who were post myocardial infarction with decreased ejection fraction (< 0.40) and had ventricular ectopy (at least 6 premature beats/hour). The most notable change in this study was that a placebo-controlled, low dose two-week run in phase was substituted for the open-labeled active titration phase of CAST I. Early drug related mortality could be determined during this two week run-in period. In CAST II there were 17 of the 665 subjects randomized to moricizine who died within the first two weeks of beginning drug treatment, compared to only 3 of 660 placebo controls (a adjusted two-tailed t-test of $p<0.02$; after adjustment for sequential monitoring). Twelve of the moricizine patients died within the first week of the start of treatment with several deaths occurring within 1 or 2 days.

From the experience of both the CAST I and CAST II studies, sodium channel blockers, particularly when used in treating subjects who have sustained a myocardial infarction and have ventricular ectopy are at increased risk of death or aborted sudden death. Based on the data from CAST II this risk is cumulative to the duration of exposure and can be discerned after even one or two days.

Overall Adverse Event Profile.

It is clear that Dolasetron is a sodium channel blocker and it is also clear that sodium channel blockers, at least in patients who have survived a myocardial infarction and have decreased ventricular function and excessive ventricular ectopy, lead to adverse outcome. Is there an excess of cardiovascular events in those treated with Dolasetron?

I've reproduce the cardiac adverse event profile that occurred within the first 24 hours as per sponsor (table 2-85 p S2-V1.3-P250). The profile is neither entirely benign nor particularly of concern. The Dolasetron group represents the summation of all doses, both those that were sub-therapeutic as well as those that are proposed for use. The data includes both normals, individuals enrolled for PK/PD studies as well as subjects treated for the proposed underlying indications.

There are several additional caveats to the interpretation of this data. First, it is likely that the frequency of cardiovascular events are under-reported. Cardiac monitoring was limited to fixed-timed ECGs and not Holters. These ECGs, moreover, were often not timed to capture peak drug effects, more often than not the ECGs were done at baseline and at 24 hours. Consequently, rhythm disturbances

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[2]The Cardiac Arrhythmia Suppression Trial II Investigators " Effect of the Antiarrhythmic Agent Moricizine on Survival After Myocardial Infarction" New Eng. J. Med. 327: 4 227-232 ; 1992.

were likely missed and the total event rate should be considered as a lower bound to the true event rate.

It could well be argued that even the rhythm disturbances which were captured were asymptomatic events, and any events which were not captured were of no clinical significance. This reviewer, however, is somewhat skeptical that all important rhythm disturbances were captured. Common manifestation of rhythm disturbances include: lightheadedness, dizziness, syncope and seizures. Events of this type were infrequent in the data base, but did occur both in the Dolasetron treated group as well as in the positive control treated group. In the absence of documentation of the rhythm at the time of the adverse event there is no way to decide if these events represent rhythm disturbances or are manifestations of the CNS effects of this drug.

There were 2 deaths within 24 hours in the Dolasetron group, with an additional death occurring within 48 hours. All deaths occurred during the prevention of chemotherapy induced nausea and vomiting. I do not have the CRFs. Sponsor's tables 2-94and 2-95 (p S2-V1.3-P296-P300), however, lists one of these as a sudden death(pt 73147-#-S-082,082-043A; dose was 1.8 mg/kg iv.[3]); a second was listed as a pulmonary embolism (pt # 73147-3-S-093,093-110/A; dose was 2.4 mg/kg iv.[4]). The death that occurred between day 2 and 3 was attributed to acute pulmonary edema (pt # 73147-3-S-081, 081-212/C; dose was 1.2 mg/kg iv[5]).

Other cardiac events appear to be proportionately distributed between Dolasetron and the other treatments or controls (there were 3.8 fold more subjects on Dolasetron when compared to the sum of the other treatments). There were 3 subjects who had ventricular arrhythmias and 8 subjects who had arrhythmias were all in the Dolasetron treated group.

Table 2. Cardiac Adverse Events During the First 24 hours (sponsor's table 2-85 p S2-V1.3-P250)

	CCNV			CCNV		PONV Prevention			PONV treatment		PONV Prevention		Total Patients			
Adverse Event Preferred Term	IV meto	IV Onda/ Grani	IV Dole	Oral Onda	Oral Dol	IV Place	IV Onda	IV Dola	IV Place	IV Dola	Oral Plac	Oral Dola	Plac	Meto	Onda /Gra	Dc
n=	193	356	2265	83	943	547	132	1785	192	765	231	936	970	193	571	669

[3]This subject was treated for a non-Hodgkin's lymphoma. The subject received previous chemotherapy including 320 mg of doxorubicin. The subject was found dead 7.5 hours after receiving Dolasetron.

[4] This subject had a history of malignant melanoma with pulmonary, brain and skin metastases. The diagnosis was made based on low partial pressure of oxygen, no statement was made that this was a change in oxygenation for this patient. No ECG during the course of the event was recorded. No autopsy was performed. The subject had a history of arrhythmia treated with flecainide. From the description it is unclear if the subject was still receiving flecainide.

[5] Patient was treated for a solid head and neck tumor with lung metastases. The patient had an initial episode of dyspnea within three hours of the Dolasetron, the dyspnea resolved only to re-occur 27 hours after receiving study medication. No ECGs were performed.

Deaths†			2 0.09%													2 0.03
TdP																
Cardiac Arrest																
Severe Bradycardia, Heart Block, or Bundle Branch Block Requiring Temporary or Permanent Pacemaker+																
Syncope		2 0.56%	2 0.09%			1 0.18%		3 0.17%		1 0.13%			1 0.1%		2 0.35%	6 0.09
All BBB		2	5		1		1			1		3			3	10
LBBB (old or new)		1 0.28%	2§§ 0.09%		1 0.11%		1 0.76%					1 0.11%				4 0.06
RBBB (old or new)		1 0.28%	2 0.09%							1 0.13%		1 0.11%			1 0.18%	4 0.06
BBB indeterminate			1 0.04%									1 0.11%				2 0.03
Second Degree AV block			2++ 0.09%													2 0.03
AV block					1 0.11%											1 0.01
Severe Bradycardia with Cardiac Pause						1^ 0.01%					2 0.87%	1 0.11%	3 0.31%			1 0.01
Orthostatic Hypotension		1 0.28%	2 0.09%		3 0.32%	2 0.37%		5 0.28%	1 0.52%	1 0.13%			3 0.31%		1 0.18%	11 0.16
Hypotension	7 3.6%	3 0.84%	26 1.1%		6 0.64%	11 2.0%	4 3.0%	23 1.3%		8 1.0%	15 6.5%	62 6.6%	24 2.5%	7 3.6%	7 1.2%	12 1.9
Bradycardia		10 2.8%	40 1.8%		42 4.5%	68 ¶ 12.4%	10 7.6%	232 13%	15 7.8%	40 5.2%	23 10%	75 8.0%	106 10.9%		20 3.5%	42 6.4
Tachycardia	3 1.6%	13 3.7%	65 2.9%	2 2.4%	21 2.2%	9 1.6%		20 1.1%	3 1.6%	10 1.3%	2 0.87%	13 1.4%	14 1.4%	3 1.6%	15 2.6%	12 1.9
SVT/PAT			1§ 0.4%													1 0.1
Atrial Flutter/Fib		2# 0.6%	3# 0.13%							1** 0.13%					2 0.35%	4 0.6
Ventricular Arrhythmia‡‡					3a 0.32%											3 0.4
Arrhythmia‡‡			5 0.22%		2 0.21%					1 0.11%						8 0.12
Nodal Arrhythmia			1 0.04%								3 1.3%	6 0.64%	3 0.31%			7 0.1

Atrial Arrhythmia Primarily PAC	7 2.0%	22 0.97%		14 1.5%	5 0.91%		9 0.5%	2 1.0%	6 0.78 %			7 0.72%		7 1.2%	51 0.76%	
Wandering Pacemaker												1 0.11%				1 0.1
Cardiac Failure			1 0.04%													1 0.1
Cardiogenic Shock																
Cardio-myopathy		1 0.28%	1 0.04%												1 0.18%	1 0.01
Cardiac Tamponade																
Myocardial Infarction		1 0.28%	1 0.04%												1 0.18%	1 0.01
Myocardial Ischemia			1 0.04%								1 0.43%	3 0.32%	1 0.1%			4 0.06
CVA																

Abbreviations used meto=metoclopramide; Onda=Ondansetron; Grani=Granisetron; Place=placebo; CCNV=Cancer Chemothera Nausea and Vomiting; PONV-Post-operative nausea and vomiting; PAC-premature atrial contraction; SVT/PAT=Supraventricu Tachycardia/paroxysmal atrial tachycardia

†Of the deaths listed in this table, an adverse event for death was reported for Patient 73147-3-S-082, 082-043/A

‡This event is not a preferred term.

+ Second degree SA block, Mobitz type I and II were reported in two Dolasetron mesylate patients; however, these events were coded econd degree AV Block. Subsequently, both events were reread by a consultant cardiologist, Craig Pratt, MD as most likely to be block ACs (MCPR0031, 008-012) and second degree AV-block, Mobitz Type I (MCPR0031, 0142-0101)

§§Baseline heart rate for Patient MCPR0032, 0107-0207 was 53 bpm. At time of LBBB, heart rate was 66 bpm. At 24 hours, heart rate w 64 bpm and LBBB was still present. Patient 73147-2-C-024, 025-010 exhibited findings of LBBB and supraventricular tachycardia w aberrancy on the 24 hour post dose ECG after receiving Dolasetron mesylate. These findings were not reported as adverse events.

^Patient 73147-2-S-087, 087-301/D experienced left anterior hemiblock

‖ Patient 73147-2-S-080,080-75/A experienced sever bradycardia with a brief cardia pause. Since this event is found under the preferr term, bradycardia, in the adverse event listings the patient is included in both rows. Patient 73147-2-S-095, 095-0675 received place and experienced bradycardia with a 20 second period of asystole. Patient AN-PO-0292, 010-0290 received Dolasetron mesylate a experienced atrioventricular dissociation. The circumstances of these adverse events, coded to AV Block, bradycardia, and A Dissociation, respectively, have been described to consultant cardiologist, Craig Pratt, MD and he recommend that these events are b collapsed categorically under severe bradycardia with a brief cardiac pause and therefore are not found in this table under the preferr term to which they were coded.

§Baseline HR for Patient MCPR0032, 0107-0207, was 53 bpm. At time of LBBB, heart rate was 66 bpm. At 24 hours, heart rate was bpm and LBBB was still present. Patient 73147-2-C-024, 025-010 exhibited findings of LBBB and SVT with aberrancy on the 24 hc post dose ECG after receiving Dolasetron mesylate. These findings were not reported as adverse events.

Patient 73147-3-S-093, 093-084C received Grani and experienced atrial fibrillation which was not reported as an adverse event. Patie 7312 7-2-C-017, 021-013 received Dola and experienced atrial fibrillation which was not reported as an adverse event.

**Atrial fibrillation was present on the 12-lead ECG for patient MCPR0044, 0260-0020 two hours after Dola this patient had al received Onda and promethazine for rescue approximately 20-25 minutes after Dola administration.

a Patient 73147-2-S-087, 087-001/B experienced ventricular premature beats which was coded to ventricular arrhythmia.

‡‡ The preferred term, ventricular arrhythmia, includes the CRF verbatim, ventricular arrhythmia, ventricular premature beats and m alterations in ventricular repolarization. The preferred term, arrhythmia includes the CRF verbatim, irregular radial pulse, irregu cardiac rate noted on post exam, irregular heart rate, arrhythmia, and slightly irregular pulse.

Dose Response Considerations to Cardiac Adverse Events:

The adverse events that are combined together in Table 2 are from heterogenous patient populations. The data were generated by combining the outcomes of multiple protocol designs (controlled and uncontrolled) from multiple study sites (including different continents and countries) and include a wide variety of doses (both subtherapeutic as well as useful). I've taken the data, as tabulated by the sponsor for the various indications and within the various indications for the US (or North American) and non-US data bases to explore whether there are increases in cardiovascular events as a function of dose.

The five distinct indications, with five separate dose response relationships for adverse events are tabulated below. For the oral formulation the two indications are 1) prevention of post-operative nausea and vomiting and 2) prevention of chemotherapy induced nausea and vomiting. For the intravenous formulation there are three indications; 1) prevention of chemotherapy induced nausea and vomiting, 2) prevention of post-operative nausea and vomiting, and 3) treatment of post-operative nausea and vomiting.

The range of the oral doses of Dolasetron were dependent on the particular indication, with a maximum dose of 200 mg for the prevention of cancer chemotherapy nausea and vomiting and 100 mg for prophylaxis of post-operative nausea and vomiting. For the intravenous formulation, doses were either administered on a mg/kg basis for the prevention of cancer chemotherapy nausea and vomiting and the prevention of post-operative nausea and vomiting. The drug was also dosed on a milligram basis for treatment of post-operative nausea and vomiting, For this last indication the mean weight for males was approximately 80 kg, so the dose, on a mg/kg basis was approximately 1.2 mg/kg. For females the median weight was 67 kg, the dose was approximately 1.3 mg/kg.

Below is a tabulation of the specific populations and the dose related adverse event profiles. The data bases of normals or populations that were studied for other indications (i.e. patients with radiotherapy-induced nausea and vomiting, acute migraine, nicotine/smoking cessation as well special populations that were treated for the purpose of pharmacokinetic analysis) are not included in these tables.

The tables below are limited to adverse events. There is no doubt, however, that Dolasetron causes dose-related increase in PR, QRS and QTc intervals, and likely also increases the JTc interval. Unless these changes resulted in specific adverse events, they were not included within the table.

I've shaded those events that appear to be increasing in a dose-related fashion. Those that are heavily shaded show a positive trend effect (as analyzed by Dr. Kooros Mahjoub using the Cochran-Armitage Trend Test), those that are lightly

shaded marginally trended to significance (2-tailed test between 0.05 and 0.1). Placebo information was used in calculating trend effects. Data for the active controls are also included within the table, but were not used in determining trend effects.

Dose-related trends were not apparent in those studies which the maximum dose was limited to 100 mg daily. For the oral formulations, for the prophylaxis of chemotherapy induced nausea and vomiting, a positive trend effect was noted in the US studies but not in the non-US studies. There was a positive dose -response trend for dizziness. There were no trends in the post-operative nausea and vomiting data base.

With respect to the intravenous doses, in the prophylaxis of chemotherapy induced nausea and vomiting, there was a positive dose-response trend to overall adverse events in the US studies and the all rate and rhythm category that consisted of data from the combined controlled data base. The statistical significance was largely due to the high event rate in the 2.4 mg/kg dose group.

In summary, there is some suggestion, but not an overwhelmingly strong signal, that there are dose related increases in adverse events with Dolasetron.

I. Oral Indications:

able 3. Prophylaxis of Chemotherapy Induced Nausea and Vomiting (Data derived from Volume A1.3 pp 108 and 110)

	Ondansetron	Dolasetron (mg)			
		25	50	100	200
US Studies Overall	N/A	88/155 (57%)	84/163 (52%)	92/151 (61%)	104/158 (66%)
Non US studies Overall	30/83 (36%)	20/80 (25%)	30/80 (38%)	30/76 (40%)	27/80 (34%)
Headache (Both)	*12/83 (15%)*	*42/235 (18%)*	*39/243 (16%)*	*52/227 (23%)*	*55/238 (23%)*
Dizziness (Both)	0/83 (0%)	5/235 (2%)	5/243 (2%)	7/227 (3%)	11/238 (5%)

Table 4 Prophylaxis of Post Operative Nausea and Vomiting (Data derived from Volume A1.3 pp 152-154)

	Placebo	Dolasetron			
		25	50	100	200
European	47/156 (30%)	51/159 (32%)	49/166 (30%)	46/154 (30%)	41/158 (26%)
Canadian	35/75 (47%)	48/76 (63%)	44/74 (60%)	38/74 (51%)	37/75 (49%)
All Heart Rate and Rhythm	28/231 (12%)	35/235(15%)	29/240 (12%)	25/228 (1%)	22/233 (9%)
All Cardiovascular general	21/231 (9%)	18/235 (8%0	27/240 (11%)	18/228 (8%)	24/233 (10%)

II Intravenous Indications:

ble 5. Prophylaxis of Chemotherapy Induced Nausea and Vomiting (Data derived from Volume A1.3 pp 129- 133)

	Metoclopramide	Ondansetron /Granisetron	Dolasetron Mesylate (mg/Kg)			
			≤ 0.6	1.2	1.8	≥2.4
US Controlled	47/201 (20%)	131/206 (63%)	174/284 (61%)	50/63 (79%)	238/358 (67%)	239/324 (74%)
Non-US Controlled	41/173 (45%)	68/150 (45%)	N/A?	73/188 (39%)	166/337 (49%)	88/161 (55%)
Uncontrolled	N/A	N/A	50/58(86%)	13/20 (65%)	32/36 (89%)	64/77 (83%)
All Heart Rate and Rhythm Controlled	8/193 (41%)	60/356 (17%)	28/284 (10%)	17/251 (7%)	92/695 (13%)	108/485 (24%)
ALL Tachycardia	3/193 (2%)	13/356 (4%)	8/284 (3%)	0	21/695 (3%)	32/485 (7%)
ALL Cardio-vascular General	21/193 (11%)	28/356 (8%)	15/284 (5%)	11/251 (4%)	51 /695 (7%)	36/485 (7%)

Table 6. Prophylaxis of Post-Operative Nausea and Vomiting (Data derived from Volume A1.3 pp 171 and 172)

	Placebo	Ondansetron	Dolasetron Mesylate Dose (mg)			
			12.5	25	50	100
US Studies	190/365 (52%)	N/A	170/365 (47%)	191/360 (53%)	185/367 (50%)	105/208 (51%)
Non-US Studies	47/182 (26%)	35/132 (27%)	18/54 (33%)	45/188 (24%)	42/184 (23%)	14/59 (24%)
Heart Rate and Rhythm US Studies	118/365 (32%)	N/A	103/365 (28%)	122/360 (34%)	107/367 (30%)	54/208 (26%)
Heart Rate and Rhythm non-US Studies	16/182 (8%)	13/132 (10%)	0/54 (0%)	10/188 (5%)	10/184 (5%)	0/59 (0%)
Bradycardia(both)	68/547 (12%)	10/132 (8%)	59/419 (14%)	84/548 (15%)	63/551 (11%)	26/267 (10%)
T-wave Changes (both)	28/547 (5%)	0/132 (0%)	27/419 (6%)	27/548 (5%)	31/551 (6%)	19/267 (7%)
Headache (both)	37/547 (7%)	5/132 (4%)	39/419 (9%)	39/548 (7%)	49/551 (9%)	27/267 (10%)
Dizziness (both)	18/547 (3%)	1/132 (1%)	25/419 (6%)	21/548 (4%)	22/551 (4%)	13/267 (5%)

Table 7 Treatment of Post Operative Nausea and Vomiting (Data derived from Volume A1.3 pp 188-189)

	Placebo	Dolasetron Mesylate Dose ((mg)			
		12.5	25	50	100
US Study	66/121 (55%)	67/130 (52%)	52/119 (44%)	55/124(44%)	61/126 (48%)
Non-US Study	13/71 (18%)	12/66 (18%)	10/65 (15%)	20/67 (30%)	16/68 (23%)
Combined Heart rate and Rhythm	42/162 (22%)	38/196 (19%)	30/184 (16%)	34/191 (18%)	42/194 (22%)
Combined Headache	14/192 (7%)	19/196 (10%)	14/184 (8%)	17/191 (9%)	21/194 (11%)
Combined Dizziness	5/192 (3%)	9/196 (10%)	12/184 (7%)	3/191 (2%)	7/194 (4%)

Cardiovascular adverse events, limited to rhythm changes in the higher dose groups.

An alternate way of looking at the data, is to consider the cardiovascular events, limited to the higher doses of Dolasetron. Below is the data, as collected and tabulated by the sponsor. I have taken the numbers directly from the sponsor's data (there is an apparent discrepancy between the denominators in this data base and those from summing the data from the above tables [6]). There appears to be increases both in PAC and PVCs for Dolasetron, relative to comparators. Palpitations were actually less frequent in the Dolasetron group. Serious rhythm disturbances appeared to be similar but slightly more frequent in the high dose Dolasetron treated group.

Table 8. Rhythm and Rate Disturbances High Dose Dolasetron

	Oral dolasetron 200 mg or iv dolasetron > 1.8 mg/kg	Positive control either iv or p.o.
PAC	25/1911 (1.3%)	7/985 (0.7%)
PVC	35/1911 (1.8%)	8/985 (0.8%)
palpitations	8/1911 (0.4%)	6/985 (0.6%)
Serious rhythm Disturbances : AFIB/ FL or Vent fibrillation or Nodal Rhythm	11/1911 (0.6%)	4/985 (0.4%)

In summary, there is only a weak signal that adverse events, in general, and cardiovascular adverse events, in specific, are increased in those treated with Dolasetron either when considering the dose response data or comparing higher dose dolasetron to concurrent positive controls. Minor rhythm disturbances such as PACs and PVCs were apparently increased in those receiving higher doses Dolasetron relative to positive controls. There were too few serious rhythm disturbances to determine if such events are increased in Dolasetron relative to positive controls.

Are adverse events more frequent among those with cardiovascular diseases at baseline?

The sponsor submits a listing of 638 subjects patients that they considered to have underlying cardiovascular disease who were treated with oral doses of Dolasetron of 200 mg or intravenous doses of $\geq$ 1.8 mg/kg. The underlying cardiovascular disease ranged from simple hypertension, with or without hyperlipidemia (N=287- my count), to subjects with objective evidence of coronary artery disease such as previous angioplasty, CABG, myocardial infarction or angina (n=120- my count). The remaining 231 subjects were described as having arrhythmia, peripheral vascular disease, coronary artery disease or endocardial valvular disease.

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6 The numbers as submitted by the sponsor are in some way incompatible with the previous table 1). In the previous table , PVCs were only infrequently noted under the composite of arrhythmias and ventricular arrhythmias there were a total of 11 such entries. In this data base there were 35 entries for PVCs alone. It is possible that many such episodes were not considered as adverse events. This discrepancy need to be resolved by the sponsor.

Among those who received 200 mg of dolasetron orally, the sponsor lists 134 patients with cardiovascular disease at baseline. Of these only 19 patients had convincing evidence of disease such as history of myocardial infarction, angioplasty, CABG or angina. A total of 53 subjects had their cardiovascular disease limited to hypertension. The remaining 62 subjects were described as having arrhythmia, peripheral vascular disease, coronary artery disease , endocardial valvular disease.

There did not appear to be an excess of cardiovascular events in those with a history of MI, CABG, angioplasty or angina. I counted 6 episodes of PVCs or PACs plus 1 subject who sustained an Myocardial infarction; rates consistent with the treatment group as a whole.

With respect to ECG changes, I've tabulated the baseline changes, limited to effects between 1-8 hours after the dose for the 19 subject with obvious coronary artery disease.

Table 9. Changes in ECG parameters for those treated with 200 mg orally and who had objective evidence of coronary artery disease.

		Intervals changes either in msec (or msec-1/2 for Qtc and JTc)					
	Heart rate	PR	QRS	QT	QTc	JT	JTc
Mean ± SEM	-0.25 ± 2.5	13.3 ± 3.5	8.13 ± 1.93	23.6 ± 9.1	23.8 ± 7.1	1.5.4 ± 9.4	15.1 ±7.5

The above data should be interpreted with caution since baseline subtracted effects are dependent on the particular study. Large drug independent effects are observed in study # 292 smaller effect in study # 43 and # 48. The changes in parameters in this population are qualitatively similar to the population as a whole.

Are ECG changes magnified with hypokalemia?

The submission of July 29, 1997, Table 3, contains the totality of ECG data for those who the sponsor defined had low serum K+ during the course of the study. The listing included a total of 298 individuals of which 238 were treated with Dolasetron, 41 patients treated with comparators and 19 treated with placebo. The sponsor, however, idiosyncratically defined hypokalemia as a plasma level of < 4.0 meq/dl.

Limiting the analysis to those with a K+ < 3.5 meq/l, there are a total of 189 subjects who received either Dolasetron, positive controls or placebo. Among these subjects, 52 received some form of potassium supplementation, so 137 subjects had K+ < 3.5 meq/l and no potassium supplementation. Of these 137 subjects, only 33 such subjects had ECG measurements at baseline and at less than 24 hours of treatment (i.e during the time drug would be anticipated to have some effect). Of these, 10 were on placebo or comparator, an additional 9 were on oral doses of 100

mg or less of Dolasetron and one received a low intravenous dose of Dolasetron (0.3 mg/kg).

There were two subjects who received Dolasetron 200 mg orally, four, six and one subjects who received intravenous doses of 1.8, 2.4 mg/kg and 5 mg/kg, respectively. Among these 13 subjects, the mean increase in QTc was 20 msec $^{-1/2}$ with a SE of 12 msec $^{-1/2}$. Five of the 13 subjects had increase in QTc of $\geq$ 40 msec (+ 95, + 64, + 59, + 47 and + 40 msec $^{-1/2}$) with the greatest increase of 95 msec $^{-1/2}$ (from 416 to 511 msec $^{-1/2}$). One subject on the other hand had a QTc decrease of -85 msec).

In summary, the data base for the use of Dolasetron in subjects with true uncorrected hypokalemia is small. These subjects were screened at baseline for electrolyte imbalances, with these balances often corrected. This reviewer would, therefore, recommend that any electrolyte abnormality be corrected prior to the use of Dolasetron.

Recommendations.

Both the sponsor and this reviewer acknowledge that Dolasetron is a cardiac sodium channel blocker both in human and animals. In guinea pig papillary muscle, the sodium channel characteristics are similar to Class Ic antiarrhythmics.

The overall exposure to Dolasetron included approximately 7000 patients and normals with the vast majority treated only with a single dose. Concurrent controls included over 1700 subjects treated either with placebo or positive controls including metoclopramide, ondansetron or granisetron. Comparatively, the safety profile of Dolasetron was not remarkably different from the composite positive controls. Cardiac monitoring, however, during treatment was sufficiently porous so that rhythm disturbances could well be missed. At higher doses there appeared to be more atrial and ventricular ectopy, mostly PACs and PVCs.

Below is a table of possible regulatory actions. Any would be reasonable though some more rational than others.

Possible Action	Rationale	Critique
Disapprove Drug	Since other drugs are available without sodium channel blocking properties why approve?	Difficult to rationalize with no obvious serious adverse events that stand out.
Approve only as second line drug.	There is no reason to believe that this drug would work where other 5HT$_3$ blocking drugs don't work. So why approve it as a second line drug.	See above.
Limit dose range to as low as possible	There is a small trend towards increase adverse events with increasing doses.	Insufficient signal that serious adverse events are dose related.

Limit higher dose, particularly for CCNV only when lower dose on previous exposures was insufficiently active.	Not a crazy idea but the study designs would not clearly allow this extrapolation	Again, limiting the exposure is not supported by a sufficient safety signal.
Contraindicate in patients with •underlying cardiac disease. •high exposure to anthracyclines •abnormal baseline electrolytes	Modest empirical data base does not really rule out increased cardiovascular risk .	I don't think the signal is sufficiently strong to recommend this tactic.
Recommend constant monitoring during first 24-hours after dose	Theoretically a rationale approach but no data to support it.	I don't think the signal is sufficiently strong to recommend this tactic.
Recommend use only as inpatient with or without monitoring	No data to suggest that multiple day treatment is effective, yet some MDs might be tempted to treat prophylactically as an outpatient,	I think it is reasonable to include such information within the labeling
Black Box CAST WARNING	Consistent with labeling of other sodium channel blockers but the population to be treated with Dolasetron are not equivalent to the population with adverse outcomes in CAST I and II.	Population to be treated with Dolasetron only minimally overlaps CAST population.
WARNING consistent with CAST I but absent a black box.	Consistent with data -Indicating only that there is a theoretical risk that cannot be ruled out by the data base.	This is a reasonable approach
WARNING consistent with CAST I but absent a black box.but extending WARNING to include high anthracycline exposure	Theoretically reasonable. Single sudden death occurred in subject with high anthracycline exposure.	Is one adverse outcome enough for this labeling?
PRECAUTION consistent with CAST I but absent a black box.	The theoretical risk of this drug as a sodium channel blocker is a reasonable parameter to base a decision to use this drug.	This is a very reasonable approach
PRECAUTION statement consistent with the CAST I warning to include patients with high anthracycline exposure.	The theoretical risk of this drug as a sodium channel blocker is a reasonable parameter to base a decision to use this drug. Single sudden death occurred in subject with high anthracycline exposure.	This is also a reasonable approach
Under Dosage and Administration: A statement that electrolytes should be checked and if necessary corrected prior to the use of Dolasetron	Consistent with study design.	This is a reasonable approach.

cc: Orig
Consult File
HFD-110 Akarkowsky
HFD-180 HGallotorres