CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020624

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

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 95215-6300,
a wholly-owned subsidiary of
Hoechst Marion Roussel, Inc.
Marion Park Drive
Kanss 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 20–624 is being submitted for approval, February 20, 1996, 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

EXCLUSIVITY SUMMARY for NDA # 20-624 SUPPL #_____

Trade Name Anzemet Injection 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 /_x_/

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).

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 /___/

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

APPEARS THIS WAY ON ORIGINAL

/S/ 9-10-97

Signature of Division Director Date

Acting

APPEARS THIS WAY ON ORIGINAL

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

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-624 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

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

Applicant Hoechst Marion Roussel INC 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 & treatment of postoperative 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.

___ 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. See attached *

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

Hoechst Marion Roussel, Inc.

NDA 20–624

dolasetron mesylate injection

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

9 Feb 96

Elaine Waller, PharmD
Vice President, US Regulatory Affairs

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: APR 11 1997

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader HFD-110 Division of Cardio-Renal Drug Products a Karkowsky 4/8/97

SUBJECT: Labeling of Dolasetron (ANZENET) NDA 20-624

TO: Dr. S. Fredd, Director, Division of Gastro-intestinal and Clotting Drugs; HFD-180 ·

THROUGH: Dr. R. Lipicky, Director,Division of Cardio-Renal Drug Products, HFD-110 lipicky

This memo is in response to your consult request of 3/18/97.

I 've included under the WARNING section a statement that subjects with underlying cardiac disease (with the specific conditions enumerated) were excluded from clinical protocols. Since DM and DMA are likely sodium channel blockers, with the cardiac adverse event profile potentially different in a patient population with structural heart disease[1]. I think some statement in labeling is appropriate.

I agree with your penciled in comment that the ECG changes should be included under WARNINGS. It seems also appropriate from the flow of the thought processes to link the adverse events presently listed under WARNINGS with the cardiovascular changes listed under PRECAUTIONS. The underlined words are my additions the ~~strikeout words are edited out~~.

WARNINGS:

ANZEMET can cause ECG changes (PR and QTc prolongations, and QRS widening) in healthy volunteers and patients. Patients, however, with underlying cardiac disease such as.(AF, CHF, previous MI???...) were excluded from clinical studies. In patients receiving chemotherapy or undergoing surgery, JT prolongations have also been observed following ANZEMET,

---

[1]Flecainide and Encainide have bad track records particularly in subjects with structural heart disease.

[2]Is this true???

ECG interval changes are related in magnitude and frequency to blood levels of the active metabolite, hydrodolesteron. ___ These changes generally mirror blood levels. Some patients, however, have interval prolongations for 24 hours or longer. Interval prolongations could lead to cardiovascular,at consequences, including heart block or cardiac arrhythmias. These have been rarely reported in patients receiving ANZEMET.

[4]Severe bradycardia with a brief cardiac pause was observed intra-operatively in a 61 year-old woman who received 200 mg ANZEMET (oral tablet) for the prevention of postoperative nausea and vomiting (PONV). This patient was also taking verapamil. Three PONV patients who received placebo also experienced severe bradycardia with a brief cardiac pause. A 66 year-old man receiving chemotherapy was found dead six hours after receiving 1.8 mg/kg (119 mg) intravenous ANZEMET injections and concomitant anthracycline therapy[5]. Vital signs taken at 1.0 and 4.5 hours after ANZEMET Injection indicated and adequate blood pressure and increased heart rate. This patient had other potential risk factors including substantial exposure to doxorubicin and concomitant cyclophosphamide. There have been no reports of severe bradycardia, heart block or bundle branch block that required a temporary or permanent pacemaker in patients receiving ANZEMET in clinical studies.

Under clinical Pharmacology:
1) I would consider summarizing the animal data. The animal data are suggestive of a effect on depolarization and repolarization.

2nd paragraph 6th line:
2) The magnitude and frequency of the ECG changes increased with dose (related to peak plasma concentrations of hydrodolesteron [6]

APPEARS THIS WAY
ON ORIGINAL

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[3]I don't know if this is true, and if true, at what doses is it true for? And if true and at relevant doses what use is it for the prescriber since normals will not be getting the drug?

[4] I presume these are accurate descriptions of the events, I have not reviewed these events.

[5]Did the sponsor ever do a retrospective analysis of the toxicity with subjects who had high exposures to anthracyclines.

[6] The parent drug is rapidly metabolized to DMA, perhaps by red blood cells and consequently, the effect of the parent drug is only of conjecture. In vitro studies suggest that the parent drug is cardiovascularly active. I would, therefore, be mute on the effect of parent drug on Qtc.

M E M O R A N D U M

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

DATE: February 5, 1997 /S/ 2/5/97

FROM: Hugo E. Gallo-Torres, M.D., Ph.D., Medical Officer, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Recommendations for Approval of DOLA•Mesyl Tablets, 100 mg

TO: Acting Director, ODE III

THROUGH: Division Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180 2/5/97 /S/

Hechst Marion Roussel, the sponsor of NDA 20-623 has submitted data in support of approval of DOLA•Mesyl tablets once-a-day for two indications: a) 200 mg given 30 min. before the start of chemotherapy, for the prevention of N&V associated with emetogenic cancer chemotherapy, including initial and repeat doses and b) 50 mg given within two hours prior to surgery, for the prevention of post-operative N&V (PONV). Review of the evidence on efficacy seemed to justify the MO recommendation for approval of DOLA•Mesyl for the prevention of PONV indication (MOR of May 31, 1996). It was recommended to approve a once-a-day dose of 100 mg (not 50 mg, as proposed by the sponsor). Both Dr. Fredd, the Division Director and Dr. Botstein the Acting Director, ODE III, agreed on this recommendation. The MO also recommended approval of DOLA•Mesyl for the prevention of CCNV indication but at a once-a-day dose of 100 mg (not 200 mg as proposed by the sponsor). The MO recommendation was based on results of pivotal trials -043 and -048 (p.335 of MOR of May 31, 1996) which supported efficacy for either 100 or 200 mg. Taking into consideration data from study -087 the Division Director selected a 200 mg dose for the prevention of CCNV indication. But this dose was not recommended for approval because of lack of sufficient safety reassurance. It was thought that, for assurance equal to that available for the proposed dose of the PONV application (100 mg) ca. 2500 more CCNV patients would need to be studied. In addition, Dr. Botstein requested further characterization of DOLA•Mesyl's cardiac effects. A comprehensive submission was made by the sponsor in response to questions about effects on EKG parameters. On December 13, 1996, a consultation request was sent to the Division of Cardio-Renal.

In the present memorandum, Dr. A. Karkowsky's recommendations in consult review of January 16, 1997, regarding the safety profile of DOLA•Mesyl, are considered. In addition to information on DOLA•Mesyl tablets (MOR of May 31, 1996) the MO incorporates brief summary statements from his recently completed review of the data from eleven trials in the DOLA•Mesyl injection NDA (MOR of

February 5, 1997). Notwithstanding cases in individual patients uncovered during the detailed review of the evidence, it can be said that, at the dose of 1.8 mg/Kg (roughly 100 mg one dose fits all), intravenously administered DOLA•Mesyl does not appear to be less safe than when this dose is administered orally. Actually, there is reason to state that at the once-a-day dose of 100 mg, the benefit/risk ratio for the intravenously administered drug may be better. The evidence at hand demonstrates that this dose of i.v. DOLA•Mesyl is effective in the prevention of CCNV induced by high dose cisplatin-based chemotherapeutic regimens and this is considered an important clinical effect. [Evaluations in high-dose cisplatin patients were not carried out with DOLA•Mesyl tablets.]

A. Efficacy

The data on which the MO's recommendation to approve the 100 mg DOLA•Mesyl tablets for both indications are based are summarized in Table 1. This information was taken from the MOR of NDA 20-623, May 31, 1996. (In both instances, ITT data are presented.) For both indications the 100 mg dose is better than the 50 mg and, as stated in Dr. Fredd's memorandum of August 16, 1996, there is no gain in using 200 mg.

TABLE 1

I. Complete Response (CR) in Prevention of CCNV Studies			
Study No.	CR With Comparator (25 mg)	DOLA•Mesyl Dose (mg) Therapeutic Gain (%)/[p-value] 50	100
-043 (n=307)	45%	27% [0.0006]	29% [0.0005]
-048 (n=320)	31%	10% [N.S.]	31% [0.0002]
II. Complete Response (CR) in Prevention of PONV Studies			
	CR With Comparator (PL)	DOLA•Mesyl Dose (mg) Therapeutic Gain (%)/[p-value] 50	100
-095 (n=793)	35%	22% [0.0001]	15% [0.0062]
0292 (n=374)	29%	11% [N.S.]	25% [0.0026]
Source of Data MOR of May 31, 1996, NDA 20-623			

B. Safety

As summarized in Dr. Fredd's memorandum of August 16, 1996, we believe the safety database is sufficient to recommend approval of the prevention of PONV indication at the 100 mg dose. The i.v. database plus the oral database provide a total of ca. 2725 patients for safety assessment [this includes 100 mg and 200 mg safety database, an approach considered appropriate]. Similarly, the MO believes that the safety database is also sufficient to recommend approval of the prevention of CCNV indication at the 100 mg dose. In the three randomized studies with the tablet formulation (-043, -048 and -087) 457 patients received doses of ≥100 mg. In the five randomized studies with the i.v. formulation (-081, -031, -093, -032 and -082), a total of 1293 patients received DOLA•Mesyl at the i.v. dose of ≥1.8 mg/Kg
single dose if patients' body weight ranged from
this dose is considered sufficient to assess the risk of the 100 mg tablets). This represents a total database of 1750 patients. [It is to be noted that Dr. Pratt's review, reproduced on page 3 of Dr. Karkowsky consult review, computes 465 patients as the number of patients receiving a single oral dose in CCNV trials and 1431 as the number of patients receiving a single i.v. dose in CCNV trials for an overall total of 1896 receiving ≥100 mg. The reason for the discrepancy in numbers is that Dr. Pratt is including additional randomized and non-randomized data.] Using Dr. R. O'Neill's table, reproduced on page 6 of Dr. Fredd's memorandum of August 16, 1996, seeing no Torsades in this number of patients would give reassurance that a 0.1% incidence would not be missed with a probability of 0.80 to 0.90.

The above computations, however, although useful for regulatory purposes, are considered rough approximations of what may or may not happen in the clinical setting, where electrolyte disbalances (K, Mg, Ca) or pre-existing arrhythmias or cardiovascular heart conditions or concomitant medications may predispose the patient to serious arrhythmias. It is important to reiterate that the clinical experience with DOLA•Mesyl is limited. Patients with arrhythmias and/or CHF were excluded from pivotal chemotherapy trials -043 and -048. The MO reiterates here that more experience is needed on the potential interaction between DOLA•Mesyl and cardiovascular medications in general and those drugs and conditions that prolong the PR, QRS and - in particular - the QT_c intervals. Also lacking are more data on possible interaction of this drug with clinical conditions involving patients with history of cardiovascular disease. But this additional information can be handled by a) appropriate language in the labeling and b) a close post-marketing monitoring of AEs in association with this drug, especially in patients in whom drugs that accumulate in and induce injury to the heart are being administered long-term, such as anthracyclines and anthracendiones.

C. Recommendations From the Cardio-Renal Consultant

In his review of January 16, 1997, the consultant concludes that the 200 mg dose of DOLA•Mesyl has "modest" (my quotes because there are cases where the changes in individual patients were very marked) effects on the cardiovascular system as judged by its effects on EKG. Listed were composite data for the three CCNV and two prevention of PONV studies with the PR, QRS, QT, QT_c and

JTc intervals from EKG points measured ca. 1 to 2h post drug. The conclusion is reached that both PR- and QRS-intervals are unquestionably increased by the drug and that QT_c but JT_c intervals are also increased. This appraisal means that although the main effects of the drug seem to be on depolarization, there also appear to be (although less frequently and less intensely) prolongations of the ventricular repolarization time [this was particularly evident in i.v. study -093]. This information should be included in the labeling.

The consultant points out that DMA, the main metabolite of DOLA•Mesyl, has a chiral center. The action of the enzyme carbonyl reductase on DOLA•Mesyl generates two isomers R-(+)- and L(-)- which co-exist at an unknown ratio in humans [in *in vitro* or *ex vivo* studies, these two isomers have been shown to possess different cardiovascular activity]. It is further pointed out that NADPH, normally produced in the hexose monophosphate (HMP) shunt is required for carbonyl reductase activity and that subjects who are G-6PD (glucose 6-phosphate dehydrogenase) deficient may be functionally limited in carbonyl reductase activity. It is speculated that these G-6PD deficient patients may be less able to clear DOLA•Mesyl, resulting in higher concentrations of the parent drug. The consultant ends up with four recommendations, two of which are as follows: 1. An analysis of the data base for those who are G-6PD deficient or alternatively should be a small study looking at the PK and PD of DM/DMA in subjects who are G-6PD deficient; 2. A study of higher single doses of DM in normals. The dose to be studied should be as high as tolerated and should be performed with adequate monitoring with trained personnel available on site, to treat any adverse events.

The MO has very carefully considered these two recommendations. These evaluations included meetings with Dr. Ahmad (who has published on the subject of G-6PD deficiency), Drs. Kauss and Pradhan (the Biopharm reviewers who, in addition, elicited an opinion from Dr. J. Collins) and Dr. L. Talarico (an expert on hematology/coagulation). Also obtained was information from up-to-date standard Biochemistry Textbooks and especially from Beck's Hematology (5^{th} Edition). The MO's assessment is succinctly summarized below.

The biochemical reaction leading to the formulation of DMA, the major active metabolite (α- and β-OH), is depicted in Fig. 1. One important piece of information is that although indeed, carbonyl reductase utilizes NADPH, being that the substrate is an aliphatic ketone, reduction could also be accomplished by **NADH-dependent** enzyme systems [K.C. Leibman, Xenobiotica 1:97 (1971); D.L. Felsted and N.R. Bachur, Mammalian Carbonyl Reductases, Drug Met. Rev. 11:1-60 (1980)]. The source of NADH cofactor of several oxidation-reduction reactions is glycolysis. This means that, for the metabolism of DOLA•Mesyl, NADPH deficiency may be clinically irrelevant since disturbances of glycolysis are extremely rare.

Nonetheless, it is recognized that ca. 5 to 20% of utilized glucose is normally metabolized through the HMP shunt and that this pathway is concerned chiefly with the generation of reducing power. In Fig. 1, the oxidative branch reversible reactions, leading to the formation of ribulose-5-phosphate from glucose-6-phosphate are depicted. The HMP shunt is the major source of NADPH in red cells, two molecules of NADPH being produced for each molecule of glucose metabolized. Traffic through the shunt pathway increases when NADPH

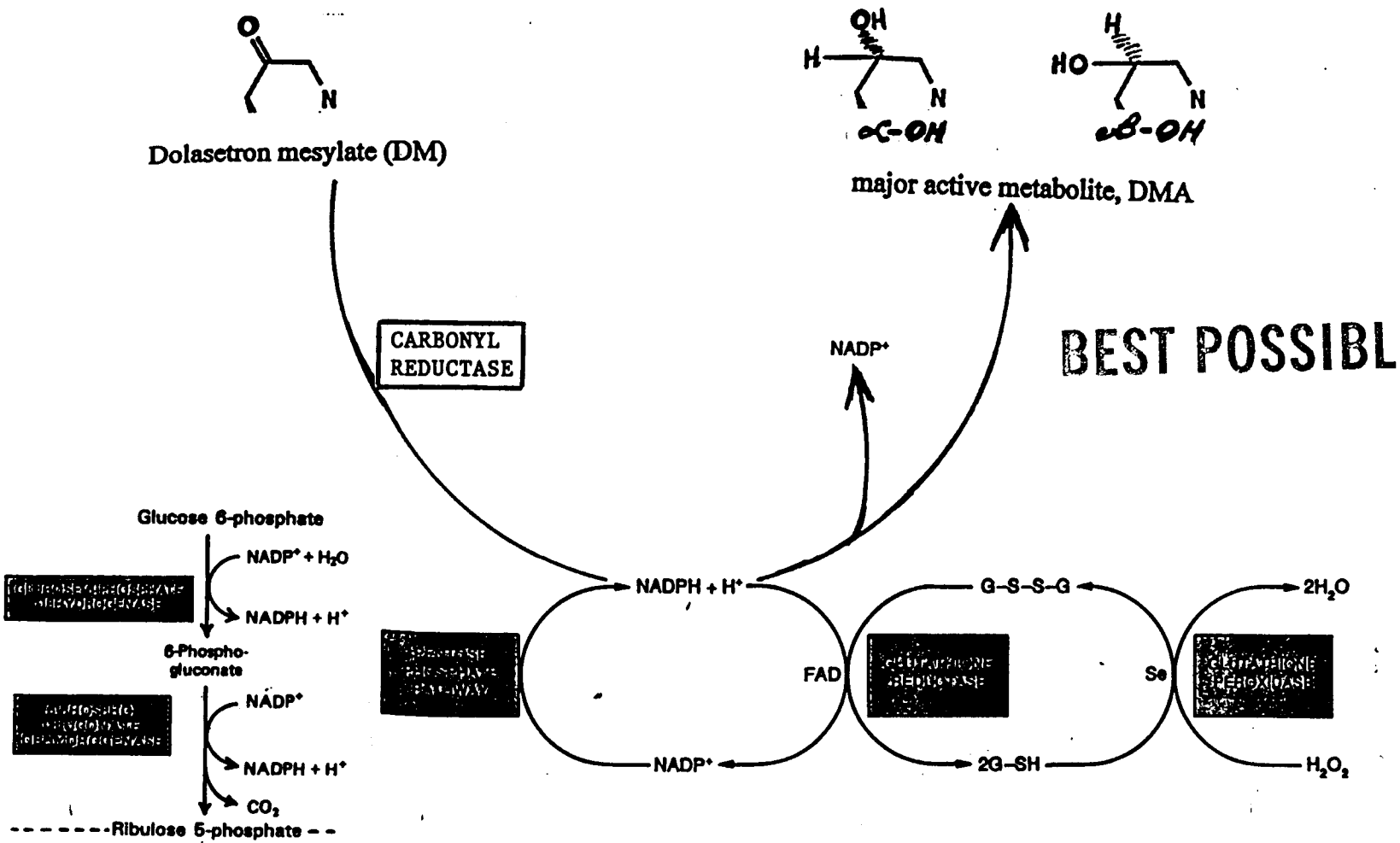

Fig. 1 - DOLA•Mesyl is converted to the major active metabolite by the action of carbonyl reductase which uses NADPH as one of its cofactors. NADPH is generated from the HMP shunt, of which, the irreversible reactions are shown.

Carbonyl reductase may also use NADH as a cofactor (not shown in scheme). NADH originates from glycolysis.

oxidation is accelerated. But, as shown in Fig. 1, the major reactions associated with NADPH oxidation are related to glutathione metabolism.[1] It is true that the majority of shunt defects are associated with diminished G-6-PD activity, which is accompanied by a fall in GSH levels because NADPH synthesis is diminished. Oxidants are thus free to damage cell constituents. Oxidation of Hb produces methemoglobin (in which Fe^{3+} cannot bind oxygen) and denatured Hb (in which globin has been oxidized). The latter precipates as intracellular Heinz bodies. Other aspects of the pathophysiology of the hemolysis associated with G-6-PD deficiency are beyond the scope of the present review.

It is however of interest to mention that more than 350 G-6-PD variants have been described but only a few have been sequenced and in only a few the mutation has been precisely described. It is worth mentioning that, of the known variants, the following are the most important clinically:

- Gd^B, the phenotype considered normal, is present in 70% of Caucasians.

- Gd^A is a normal variant present in 20% of American blacks. Replacement of asparagine with aspartic acid makes it electrophoretically faster than Gd^B.

- Gd^{A-}, the most common variant associated with hemolysis, is found in 11% of American blacks and in higher percentages in many African populations. Its electrophoretic mobility is identical to that of Gd^A, but its catalytic activity is impaired. Because it has two nucleotide substitutions, it may be that the A^- mutation occurred when A was the predominant genotype.

- Gd^{Med}, the second most common abnormal variant (and the most common among Caucasians), is found in many ethnic groups in the Mediterranean area basin (Italians, Greeks, Sardinians, Sephardic Jews, Arabs, etc.), and in India and southeastern Asia. Its electrophoretic mobility is normal, but its catalytic activity is markedly reduced. It may include several discrete variants.

- Gd^{Canton} is a common variant in Oriental populations that produces a clinical syndrome like that associated with Gd^{A-}.

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[1] Red cells contain a high concentration (2 mM) of reduced glutathione (GSH), a tripeptide (γ-glutamyl-cysteinyl-glycine), that is synthetized de novo by mature red cells and serves as a sulfhydryl buffer, cycling between its reduced form (GSH) and an oxidized form (GSSG), which links two tripeptides by a disulfide bond. GSH acts intracellularly to protect red cells against injury by exogenous and endogenous oxidants, such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), which are produced by macrophages in infection and by red cells in the presence of certain drugs such as primaquine. The ingestion of broad beans (also known as fava beans) **Vicia fava**, can likewise induce a hemolytic anemia in dehydrogenase-deficient people. Accumulation of these agents leads to injury of cell proteins and lipids. This is normally prevented by GSH, which inactivates such oxidants. This detoxification can occur spontaneously, but it is accelerated by **glutathione peroxidase**, a remarkable selenium-containing enzyme. As hydrogen peroxide is reduced in the peroxidase reaction, GSH is oxidized to GSSG and mixed disulfides with protein-thiols (GS-S-protein). (Catalase also degrades peroxides, but under physiologic conditions it is less important.) Regeneration of GSH is catalyzed by glutathione reductase, A flavoprotein in this NADPH-mediated reaction, both GSSG and mixed disulfides are reduced to GSH as NADPH is simultaneously oxidized. This in turn stimulates HMP shunt activity, which regenerates NADPH. The tight coupling of HMP shunt and glutathione metabolism efficiently protects red cells from oxidant injury.

The above-summarized information suggests that Gd^{A-} and Gd^{Med}, the first and second most common abnormal variants associated with hemolysis, are infrequent in the U.S. population.

On the practical side, although it is well established that blood levels of the DOLA•Mesyl metabolite DMA are associated with alterations of the EKG, efficacy of DOLA•Mesyl (the parent drug) does not seem to depend on bioconversion, since unmetabolized DOLA•Mesyl is active (efficacy wise). The consultant recommendations appear to test the hypothesis that the parent drug is the toxic species. But there is no evidence for such a proposal. It appears that the parent drug, which is rapidly and almost quantitatively converted to the metabolite, cannot be more toxic than the metabolite. The hypothesis that the G-6PD deficient patient (actually a variant of the lot) may be more susceptible to EKG alterations following administration of DOLA•Mesyl does not seem tenable. Nevertheless, as proposed by Dr. J. Collins, such a theory may be tested in cardiocytes *in vitro* (see Appendix I, Memorandum of January 31, 1997 from Dr. Pradhan to the MO).

The MO does not believe that the consultant's recommendations Nos. 1 and 2 would be helpful. It is important to mention that studies in small number of subjects have shown that doses as high as 5 mg/Kg (the equivalent of 350 mg single dose) were not accompanied by clinical cardiovascular alterations. Once again, the MO concern is not what would happen in the normal individual given the drug alone and at recommended doses, depending on indication.

On the other hand, the consultant's recommendation No. 3 ["The ECGs of all patients with large cumulative exposures to either daunorubicin or doxorubicin should be analyzed for ECG changes. In the absence of a respectable database a small study should be considered in those who are receiving high cumulative doses"] needs to be carefully considered. Anthracycline (an antileukemic antibiotic; ex. daunorubicin) accumulates in the heart muscle where it induces cardiac toxicity through degeneration and atrophy of cardiac muscle in the area around His's bundle. As pointed out in MOR of May 31, 1996 of NDA 20-623, there is little experience in patients that had been treated with adriamycin long-term and the concomitant administration of DOLA•Mesyl. This situation is compounded by the occurrence of a sudden death reported in NDA 20-624 (DOLA•Mesyl injection). This occurred in a patient six hours after receiving 1.8 mg/Kg intravenous DOLA•Mesyl and concomitant anthracycle. This patient had numerous risk factors including substantial exposure to doxorubicin, prior thoracic irradiation and concomitant cyclophosphamide. But, as pointed out by Dr. C.R. Benedict in his Cardiovascular Export Report for Dolasetron, "there is no way to exclude a causal relationship between dolasetron exposure and this death". The MO recommends that information on this death be succinctly included in the labeling. The MO concludes that there is need for close patient monitoring during DOLA•Mesyl therapy in patients that have received long-term anthracyclines, anthracendiones or other drugs that accumulate in the heart and induce cardiac arrhythmias).

As per consultant's recommendation 3, the sponsor should be asked to analyze the EKGs of all patients with large cumulative exposures to either daunorubicin or doxorubicin for EKG changes. Since a succinct description of

the sudden death in a patient receiving intravenous DOLA•Mesyl and anthracycline and that of complete block in another patient receiving 200 mg of DOLA•Mesyl tablets and verapamil are to be included in the labeling, there seems to be no need to ask the sponsor to consider a "small study in those who are receiving high cumulative doses".

D. Labeling Recommendations

On pages 8-9 of the Consult, the consultant states "I am presuming that warnings or precautions, about the use of this drug in such a population would of course appear prominently in labeling". The consultant is making reference to the following paragraph at the bottom of page 8 of his Consult Review:

> "Aside from those who may have kinetics different from the general population, there are those whose electrocardiographic response to the usual concentrations of DM and DMA may be excessive. Subjects with underlying cardiovascular disease, those with aberrations of electrolytes, those treated with concurrent drugs that modify cardiac conduction may have excessive ECG responses to DM. Unfortunately, all clinical studies excluded subjects with underlying cardiovascular disease, rhythm disturbances that required antiarrhythmic therapy, or those with abnormal ECG intervals at baseline. It is, therefore, unlikely that the already accumulated safety data base will adequately address whether there is a sub-population that is more sensitive to electrocardiographic alterations."

The MO agrees with Consultant's recommendation No. 4. The MO reiterates here his recommendation of including a warning and a precaution section in the labeling for DOLA•Mesyl tablets (as well as for the injection formulation).

/S/ February 5, 1997

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

cc:
NDA 20-623
NDA-20-624
HFD-180
HFD-180/SFredd
HFD-180/HGallo-Torres
r/d 2/5/97 jgw
GEN\20623701.0HG

APPENDIX I

Memorandum

To: Hugo Gallitoris, MD Ph.D.

Through: Lydia Kaus, Ph.D. /S/ 1/31/97 JAN 31 1997

From: Rajendra Pradhan, Ph.D. /S/ 1-31-97

Background: Dolasetron is an antiemetic drug under review by Division of Gastrointestinal and Coagulation Products (HFD-180). The sponsor is requesting an approval for tablet (oral) and injection (IV infusion) forms of dolasetron. Dolasetron is a pro-drug and it is converted to its pharmacodynamically active form (DMA) by an ubiquitous enzyme, carbonyl reductase. Dolasetron and DMA both exhibit cardio-toxicity (Qtc prolongation) to same extent (based on in-vitro studies). The Medical officer (MO) (HFD-180) currently considers 100 mg oral dose to be the safe and effective dose for chemotherapy induced nausea and vomiting and for PONV (for sponsor's proposed doses, refer to proposed labeling). The MO requested the DPE-II, OCPB to compare the systemic exposure at 100 mg dose for the two routes of administration.

In addition, Director of ODE-III had consulted the safety issues on Dolasetron to Division of Cardio-Renal Products (HFD-110). In the response, questions were raised regarding the conversion of pro-drug Dolasetron to DMA. Specifically, concerns were raised about the role glucose 6 phosphate dehydrogenase (G6-PD) plays in carbonyl reductase ability to reduce Dolasetron to DMA. Theoretically, in G6-PD deficiency (due to genetic reasons or administration of other drugs), Dolasetron could stay in systemic circulation for longer duration of time. This however, was not seen in the clinical data base presented by the sponsor. Currently, the MO (HFD-180) is working on this issue and invites any suggestions.

Comments:
In a pharmacokinetic comparison between IV and oral routes at the same doses, for pharmacokinetic parameters such as $AUC_{0-\infty}$ and Cmax for DMA, IV route showed about 30% greater $AUC_{0-\infty}$ and Cmax contribution than oral route. It should also be noted that there is an additional 8% contribution to $AUC_{0-\infty}$ from the prodrug component (DM) when IV is compared to oral. Since, in-vitro DM and DMA are equi-toxic, the 8% contribution from DM could be additive. In other words, **a suitable IV dose to get a similar DMA-oral exposure should be at least 30% lower than the corresponding oral dose**.

Attempts were made to do a similar comparison ($AUC_{0-\infty}$ and Cmax /IV vs. Oral) using a modeling approach. However, the predicted values showed about 8% underestimation bias (predicted Cmax lower than observed Cmax). Therefore, a noncompartmental approach was used to compare the pharmacokinetic parameters between IV and oral route.

It appears there are few questions unanswered at the current time about the conversion of prodrug to drug. These are as follows:
What is the effect of glucose 6 phosphate dehydrogenase deficiency on the carbonyl reductase that metabolizes DM to DMA?
Is carbonyl reductase, responsible for DM metabolism totally NADPH dependent?

I would advice that we ask these questions to the sponsor.

Lydia Kaus (Team Leader, DPE-II) has discussed this issue with Jerry Collins (Director, DCPR, OTR) and following suggestions were generated.

1. explore the exposure-toxicity in dogs and find out what (DM or DMA) is responsible for the QTc prolongation

2. For QTc prolongation, Dr. Collins think that the simplest test only requires cardiocytes in vitro. Woosley's group at Georgetown used this test system effectively to show that the active metabolite of terfenadine was at least 500-fold less toxic than the parent. [JAMA; 1993; vol 269, p1532]

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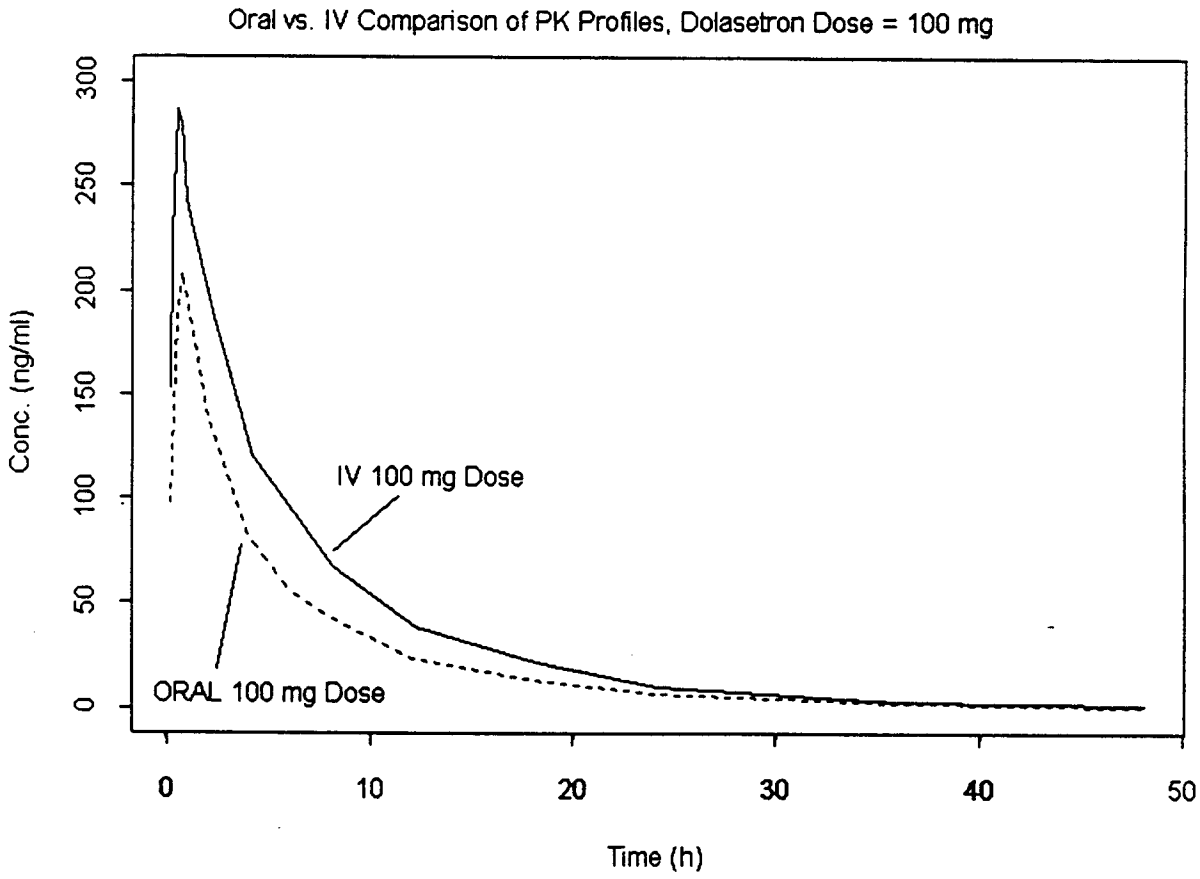
ON ORIGINAL



cc: NDA 20-623 and 20-624, HFD-180, HFD-870 (MChen, Kaus, Pradhan), HFD-850 (Drug, Reviewer), Drug File (Millison)

M E M O R A N D U M

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

DATE: February 6, 1997

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180

SUBJECT: NDA 20,624 (ANZEMET®/Dolasetron Mesylate) -
Preclinical Portions of the Labeling.

TO: NDA 20,624

The following portions of the attached sponsor's version of labeling (identified) should be replaced or expanded with the accompanying revisions/additions.

1. "PRECAUTIONS"

   a. "Carcinogenesis, Mutagenesis, Impairment of Fertility" - on sponsor's page S4-V1.13-P215.

   b. "Pregnancy

      Teratogenic Effects. Pregnancy Category B:" - on sponsor's page S4-V1.13-P215.

2. "OVERDOSAGE" - on sponsor's page S4-V1.13-P219.

Revisions

1. "PRECAUTIONS

   Carcinogenesis, Mutagenesis, Impairment of Fertility

   In a 24-month carcinogenicity study, mice (CD-1) were treated orally with dolasetron mesylate 75, 150 or 300 mg/kg/day (225, 450 or 900 mg/m^2/day). For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 3.4, 6.8 and 13.5 times the recommended clinical dose (66.6 mg/m^2, i.v.) on a body surface area basis. There was a statistically significant (p=0.0001) increase in the incidence of combined hepatocellular adenomas and carcinomas

in males treated with 150 mg/kg/day (450 mg/m^2/day, 6.8 times the recommended human dose based on body surface area) and above. No increase in liver tumors was observed at a dose of 75 mg/kg/day (225 mg/m^2/day, 3.4 times the recommended human dose based on body surface area) in males and at doses up to 300 mg/kg/day (900 mg/m^2/day, 13.5 times the recommended clinical dose based on body surface area) in females.

In a 24-month rat (Sprague-Dawley) carcinogenicity study, oral dolasetron mesylate at doses up to 150 mg/kg/day (900 mg/m^2/day, 13.5 times the recommended human dose based on body surface area) in males and 300 mg/kg/day (1800 mg/m^2/ day, 27 times the recommended human dose based on body surface area) in females was not tumorigenic.

Dolasetron mesylate was not genotoxic in the Ames test, the rat lymphocyte chromosomal aberration test, the Chinese hamster ovary (CHO) cell (HGPRT) forward mutation test, the rat hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test.

Dolasetron mesylate at oral doses up to 400 mg/kg/day (2400 mg/m^2/day, 36 times the recommended human dose based on body surface area) in male rats and up to 100 mg/kg/day (600 mg/m^2/day, 9 times the recommended human dose based on body surface area) in female rats was found to have no effect on fertility and reproductive performance."

"Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in pregnant rats at i.v. doses up to 60 mg/kg/day (5.4 times the recommended human dose based on body surface area) and pregnant rabbits at doses up to 20 mg/kg/day (3.2 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to dolasetron mesylate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

2. "OVERDOSAGE

Single i.v. doses of dolasetron mesylate at 160 mg/kg in male mice and 140 mg/kg in female mice and rats of both sexes (6.3 to 12.6 times the recommended human dose based on body surface area) were lethal. Symptoms of acute toxicity were tremors, depression and convulsions."

Jasti B. Choudary, Ph.D., B.V.Sc.

cc:
Orig. NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Fredd

JBC/hw/2/6/97
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APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020624

CORRESPONDENCE

Johnson

NDA 20-623
NDA 20-624

Hoechst Marion Roussel
Attention: Louise Shibley
Marion Park Drive, P.O. Box 9707
Kansas City, MO 64134-0707

AUG 20 1997

Dear Ms. Shibley:

Please refer to your pending September 28, 1995 and February 19, 1996 new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anzemet (dolasetron) Tablets and Injection, respectively.

In response to your request, we are forwarding you copies of the July 16 and 28, 1997 clinical statistical reviews.

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

Sincerely yours,

/S/ 8/19/97

/S/ 8-19-97

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

cc:
Original NDAs 20-623, 20-624
HFD-180/Div. Files
HFD-180/CSO/K.Johnson

Drafted by: kj/August 19, 1997/c:\wpfiles\cso\n\20623708.0kj

INFORMATION REQUEST (IR)

NDA 20-624

Hoechst Marion Roussel, Inc.
Attention: Louise Shibley
Marion Park Drive, P.O. Box 9707
Kansas City, MO 64134-0707

JUL 24 1997

Dear Ms. Shibley:

Please refer to your pending February 19, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anzemet (dolasetron) Injection.

We also refer to your amendments dated March 5 and 27, and April 9, 1997, containing chemistry information submitted in response to our February 20, 1997 approvable letter.

We have completed our review of the chemistry sections of your submissions and request that you provide the following:

1.

2.

Please provide written confirmation of your commitment to provide this information following approval (Phase 4).

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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

/S/ 7/24/97

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-624
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
HFD-180/AShaw
HFD-820/ONDC Division Director
Drafted by: kj/July 22, 1997
c:\wpfiles\cso\n\20624707.0kj
Initialed by: Eduffy 7/22/97
Ltalarico 7/22/97
INFORMATION REQUEST (IR)

NDA 20-624
NDA 20-623

Hoechst Marion Roussel, Inc.
Attention: Louise Shibley
Marion Park Drive, P.O. Box 9707
Kansas City, MO 64134-0707

JUN 11 1997

Dear Ms. Shibley:

We acknowledge receipt on March 19 and 31, 1997 of your March 18 and 28, 1997 amendments to your new drug applications (NDAs) for Anzemet (dolasetron) Injection and Tablets, respectively.

These amendments contains additional labeling information submitted in response to our February 20 and March 5, 1997 approvable letters.

We consider these major amendments under 21 CFR 314.60 of the regulations. Therefore, the due dates under the Prescription Drug User Fee Act of 1992 (PDUFA) are September 19 and 30, 1997, respectively.

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

Sincerely yours,

/S/ 6/11/97

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

/S/ 6/11/97

cc:
Original NDA 20-624, NDA 20-623
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
DISTRICT OFFICE
Drafted by: kj/June 10, 1997/c:\wpfiles\cso\n\20623706.0kj
ACKNOWLEDGEMENT (AC)

Johnson

NDA 20-624

Hoechst Marion Roussel, Inc.
Attention: Louise Shibley
Marion Park Drive, P.O. Box 9707
Kansas City, MO 64134-0707

FEB 27 1997

Dear Ms. Shibley:

Please refer to your new drug application for Anzemet (dolasetron mesylate) Injection.

In response to your February 26, 1997 request, we are forwarding copies of the clinical and statistical reviews.

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

Sincerely yours,

/S/

APPEARS THIS WAY

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

Enclosures

2/27/97
/S/

APPEARS THIS WAY

cc:
Original NDA 20-624
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
Drafted by: kj/February 27, 1997/c:\wpfiles\cso\n\20624702.2kj

GENERAL CORRESPONDENCE

Johnson

NDA 20-623
~~NDA 20-624~~

Hoechst Marion Roussel, Inc.
Attention: Louise Shibley
Marion Park Drive, P.O. Box 9707
Kansas City, MO 64134-0707

MAY 16 1996

Dear Ms. Shibley:

Please refer to your pending September 28, 1995 and February 19, 1996 new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anzemet (dolasetron) Tablets and Injection, respectively.

We have completed our review of the Environmental Assessment (EA) sections of your submissions and request the following revisions:

NDA 20-623
Your certification in item 13 predates the EA. Please submit a revised page for format item 13 that does not predate the format item 1 of the EA.

NDA 20-624
The certification of compliance from Ben Venue Laboratories, Inc. provided in your EA is for compliance with CGMPs, and is not a citation of and statement of compliance with applicable emissions requirements at federal, state and local levels. Please submit a signed statement, for inclusion in your EA, from Ben Venue Laboratories Inc. that they are in compliance with all applicable permits and regulations.

We would appreciate your prompt written response so we can continue our evaluation of your NDAs.

If you have any questions, please contact:

Kathi Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

/S/ 5/15/96
/S/ 5/15/96

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

cc:
Original NDAs 20-623, ~~20-624~~
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
HFD-180/MAdams
HFD-180/GChen
HFD-820/Yuan Yuan Chiu
drafted: kj/May 13, 1996
c:\wpfiles\cso\n\20623605.0kj
r/d Initials: GChen 5/15/96
Jgibbs 5/15/96
INFORMATION REQUEST (IR)

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Johnson

NDA 20-624

APR 17 1996

Hoechst Marion Roussel, Inc.
Attention: Louise Shibley
Marion Park Drive, P.O. Box 9707
Kansas City, MO 64134-0707

Dear Ms. Shibley:

Please refer to your pending February 19, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anzemet (dolasetron) Injection.

To complete our review of the chemistry section of your submission, we request the following:

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

APPEARS THIS WAY
ON ORIGINAL

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

/S/ 4/16/96

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

/S/ 4/17/96

cc:
Original NDA 20-624
HFD-180/Div. Files
HFD-180/CSO/K.Johnson
HFD-180/GChen
HFD-820/Yuan Yuan Chiu
drafted: kj/April 16, 1996
c:\wpfiles\cso\nm\206724604.0kj
r/d Initials: GChen 4/16/96
JGibbs 4/16/96
INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL