# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020624

## CHEMISTRY REVIEW(S)

# DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

**NDA:#** 20-624 **CHEM REVIEW #** 1 **REVIEW DATE:** January 3, 1997

**SUBMISSION TYPE**

| | DOCUMENT | CDER | DATES ASSIGNED | REVIEW |
|---|---|---|---|---|
| ORIGINAL | 20-Feb-96 | 21-Feb-96 | 06-Dec-96 | Current |
| AMENDMENT | 22-Apr-96 | 23-Apr-96 | " | " |
| | 09-May-96 | 10-May-96 | " | " |
| | 21-May-96 | 23-May-96 | " | " |

FEB - 3 1997

**NAME & ADDRESS OF APPLICANT :**

Hoechst Marion Rousel, Inc
Marion Park Drive
Kansas City, Missouri 64134

**DRUG PRODUCT NAME:**

Proprietary: ANZEMET®
Nonproprietary/USAN: dolasetron mesylate
Code Name/#: MDL 73,147EF
Chem.Type/Ther.Class: 1S antiemetic

**INDICATIONS**

1. The prevention of nausea and vomiting associated with emetogenic cancer chemotherapy including initial and repeat courses.
2. The prevention of postoperative nausea and vomiting.
3. The treatment of postoperative nausea and vomiting.

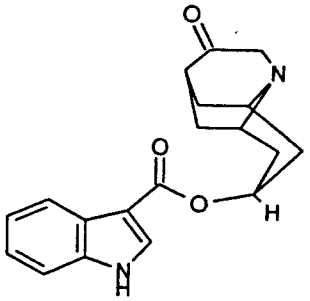
**DOSAGE FORM:** injection
**STRENGTHS:** 25 mg, 50 mg, 100 mg, 200 mg
COMMENT: The applicant lists four strengths on the Form 356h (25 mg, 50 mg, 100 mg and 200 mg. However the application describes three different strengths: 12.5 mg, 100 mg and 200 mg. The applicant should explain this discrepancy.

**ROUTE OF ADMINISTRATION:** intravenous

**HOW DISPENSED:** __X__ Rx _____ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**

(2α, 6α, 8α, 9aβ)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate monohydrate.



$\cdot CH_3SO_3H \cdot H_2O$

**SUPPORTING DOCUMENTS:**

**CONSULTS:**

| Type | Division | Date | Status |
|---|---|---|---|
| Microbiology | Microbiology Staff | Feb 27, 1996 | Acceptable (May 03, 1996) |
| Environmental Assessment | Environmental Assessment Staff | | Acceptable (FONSI June 21, 1996) |

Note that there is no statistical consult since there is only 9 months of data submitted.

**REMARKS/COMMENTS:** There are very few remaining issues. should be determined.

**CONCLUSIONS & RECOMMENDATIONS:** The application is approvable from a CMC point of view.

/S/ 1/31/97

Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 2/3/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA #20-624
HFD-180/SFredd
HFD-180/EDuffy
HFD-092/RLipov
HFD-820/JGibbs
HFD-180/Division File/ NDA 20-624
HFD-181/KJohnson
R/D Init by:
abs/**F/T/ABS 1-31-97**/WP C:\WPFILES\NG\20624612.1AS

Johnson

# DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

**NDA:#** 20-624 **CHEM REVIEW #** 2 **REVIEW DATE:** May 1, 1997

" " 21 1997

| SUBMISSION TYPE | DOCUMENT | CDER | DATES ASSIGNED | REVIEW | COMMENTS |
|---|---|---|---|---|---|
| ORIGINAL | 20-Feb-96 | 21-Feb-96 | 06-Dec-96 | 1 | IR Letter 02-Feb-97<br>AE Letter 20-Feb-97 |
| AMENDMENT | 22-Apr-96 | 23-Apr-96 | " | " | |
| | 09-May-96 | 10-May-96 | " | " | |
| | 21-May-96 | 23-May-96 | " | " | |
| AMENDMENT | 05-Mar-97 | 06-Mar-97 | 11-Mar-97 | Current | Responses to AE Letter |
| BC | 07-Mar-97 | 10-Mar-97 | 19-Mar-97 | Current | Stability data |
| BL | 27-Mar-97 | 28-Mar-97 | | Current | Draft Labeling |
| BC | 27-Mar-97 | 28-Mar-97 | | Current | Response to telecon |
| BC | 09-Apr-97 | 10-Apr-97 | 15-Apr-97 | Current | Stability analysis |

**NAME & ADDRESS OF APPLICANT :**

Hoechst Marion Roussel, Inc
Marion Park Drive
Kansas City, Missouri 64134

**DRUG PRODUCT NAME:**

| | |
|---|---|
| Proprietary: | ANZEMET© |
| Nonproprietary/USAN: | dolasetron mesylate |
| Code Name/#: | MDL 73,147EF |
| Chem.Type/Ther.Class: | 1S antiemetic |

**INDICATIONS**

1. The prevention of nausea and vomiting associated with emetogenic cancer chemotherapy including initial and repeat courses.
2. The prevention of postoperative nausea and vomiting.
3. The treatment of postoperative nausea and vomiting.

**DOSAGE FORM:** injection

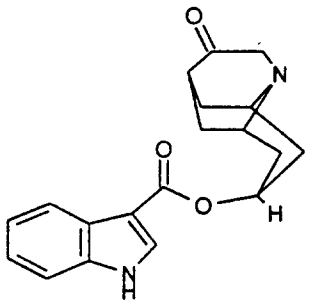
**STRENGTHS:** 25 mg, 50 mg, 100 mg, 200 mg

**ROUTE OF ADMINISTRATION:** intravenous

**HOW DISPENSED:** __X__ **Rx** _____ **OTC**

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**

(2α, 6α, 8α, 9aβ)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate monohydrate.



$CH_3SO_3H \cdot H_2O$

**SUPPORTING DOCUMENTS:**

**CONSULTS:**

| Type | Division | Date | Status |
|---|---|---|---|
| Microbiology | Microbiology Staff | Feb 27, 1996 | Acceptable (May 03, 1996) |
| Environmental Assessment | Environmental Assessment Staff | | Acceptable (FONSI June 21, 1996) |

**CONCLUSIONS & RECOMMENDATIONS:** The application may be approved with some post-approval commitments.

/S/

7/17/97

Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/

7/24/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-624
HFD-180/LTalarico 7-23-97
HFD-180/EDuffy
HFD-092/RLipov
HFD-820/JGibbs
HFD-180/Division File/NDA 20-624
HFD-181/CSO/KJohnson
R/D Init by:EDuffy/7-16-97
abs/dob **F/T 7-17-97**\WP c:\wpfiles\chem\N\20624703.2AS

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Consult #531(HFD-180)

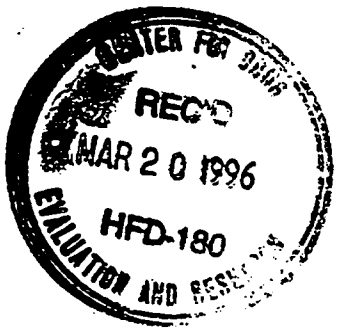
ANZEMET dolasetron tablets

A review revealed no names which sound like or look like the proposed name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

DCBoring, Chair



531

# REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: ~~Ms. Yana Mille~~, Chair, (HFD-~~611~~ 530 MPN II
Dan Boring, PhD

FROM: Division of GI + Coagulation Drug HFD- 180
Attention: Kati Johnson Phone 443-0487

DATE: ~~12/8/95~~ 12/5/95

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Anzemet Tablets NDA/ANDA# 20-623

Company Name: Hoechst Marion Roussel

Established name, including dosage form: dolasetron

Other trademarks by the same firm for companion products:
none

Indications for Use (may be a summary if proposed statement is lengthy): 1) prevention of postoperative nausea & vomiting
2) prevention of chemotherapy induced nausea & vomiting

Initial comments from the submitter: (concerns, observations, etc.)
none

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as p

May-94

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** 020624

## ENVIRONMENTAL ASSESSMENT AND/OR FONSI

# ENVIRONMENTAL ASSESSMENT

# AND

# FINDING OF NO SIGNIFICANT IMPACT

# FOR

# ANZEMET®

# (Dolasetron mesylate)

# Injection 12.5 mg ampules, 100 mg vials, and 200 mg vials

# NDA 20-624

# Division of Gastro-Intestinal and Coagulation Drug Products

# (HFD-180)

# FOOD AND DRUG ADMINISTRATION

# CENTER FOR DRUG EVALUATION AND RESEARCH

C:\WPFILES\FONSI\20624.FPV

# FINDING OF NO SIGNIFICANT IMPACT

## ANZEMET®

## (Dolasetron mesylate)

## Injection 12.5 mg ampules, 100 mg vials, and 200 mg vials

## NDA 20-624

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for ANZEMET®, Hoechst Marion Roussel has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a in accordance with format (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Dolasetron mesylate is a drug which is administered as 12.5 mg ampules, 100 mg vials, and 200 mg vials strength for injection in the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, the prevention of postoperative nausea and vomiting, and treatment of postoperative nausea and vomiting. . The drug substance is manufactured by the Dow Chemical Company, Midland, Michigan. The finished drug product is produced by Ben Venue Laboratories, Bedford, Ohio. The finished drug product will be used by patients throughout the United States.

Dolasetron that is introduced into the patient will be extensively metabolized to an active metabolite which will be further metabolized or excreted primarily in urine. The metabolites are chemically similar to dolasetron and are expected to be more polar.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at licensed incineration sites. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

6/17/96 /S/
DATE

Approved
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

6/17/96 /S/
DATE

Concurred
Nancy Sager/Acting Supervisor
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020624

## PHARMACOLOGY REVIEW(S)

NDA 20-624

NDA 20-624

NOV 29 1996

REVIEW # 1

**Reviewer**: Tanveer Ahmad, Ph.D.
Pharmacologist, HFD-180

**Sponsor and Address**: Hoechst Marion Roussel, Inc.
Kansas City, Missouri 64134

**Date of Review**: November 8, 1996

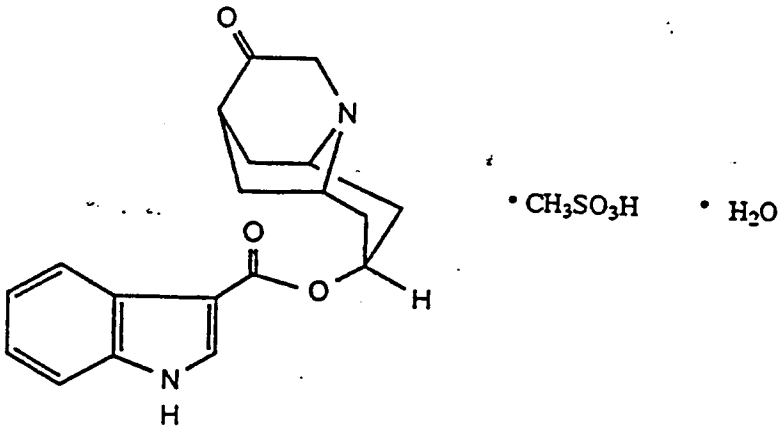
**Date of Submission**: February 19, 1996

**Date of HFD-180 Receipt**: February 21, 1996

## REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
## (Original Summary)

**Drug**: Dolasetron mesylate/MDL 73,147 EF/ANZEMET Injection

**Chemical Name**: (2α, 6α, 8α, 9aß)-Octahydro-3-oxo-2, 6-methano-2H-quinolizin-8-yl-1H-indol-3-carboxylate monomethane sulfonate, monohydrate.



$C_{19}H_{20}N_2O_3 . CH_3SO_3H . H_2O$

MW 438.50

**Formulation**: Each ml of dolasetron mesylate monohydrate (Anzemet) injection contains 20 mg of dolasetron mesylate monohydrate and 38.2 mg mannitol with an acetate buffer in water for injection

**Proposed Marketing Indication**: Anzemet is indicated for the prevention of cancer chemotherapy-induced nausea and vomiting, and prevention and treatment of postoperative nausea and vomiting.

**Dose**: The recommended i.v. adult and pediatric (2-17 years old) dose of Anzemet is 1.8 mg/kg given within 30 min prior to chemotherapy for the prevention of cancer chemotherapy-induced nausea and vomiting.

For the prevention and treatment of postoperative nausea and vomiting, the recommended i.v. adult and pediatric (2-17 years) dose of Anzemet is 12.5 mg given at cessation of anesthesia (prevention) or as soon as nausea or vomiting presents (treatment).

# PRECLINICAL STUDIES AND TESTING LABORATORIES

**Following listed studies were submitted under NDA 20-623.**

| Type of Study | Study # | Drug Lot # | Testing Laboratories | Page # |
|---|---|---|---|---|
| **Pharmacology** | | | | 5 |
| Absorption: | | | | 14 |
| Rat, rabbit, dog and monkey | | | | |
| Distribution: | | | | 20 |
| Rat | | | | |
| Metabolism: | | | | 23 |
| Rat, rabbit, dog and monkey | | | | |
| Excretion: | | | | |
| Rat, rabbit dog and monkey | | | | |
| **ACUTE TOXICITY** | | | | 29 |
| Mouse | | | | |
| Oral | C-88-0017-T | 15 | DPT | |
| I.V. | C-88-0012-T | 07 | DPT | |
| Rat | | | | |
| Oral | C-88-0017-T | 15 | DPT | |
| I.V. | C-88-0012-T | 07 | DPT | |
| Dog | | | | |
| Oral | C-88-0020-T | 15 | DPT | |
| I.V. | C-88-0013-T | 07 | DPT | |
| Monkey | | | | |
| Oral | C-88-0020-T | 15 | DPT | |
| I.V. | C-88-0013-T | 07 | DPT | |
| **Subacute/Subchronic/ Chronic Toxicity:** | | | | |
| Rat | | | | |
| 1-Month (I.V.) | I-92-0148-T | 8611093 | DIC | 31 |
| 1-Month (gavage) | C-91-0071-T | C-46711 | DPT | 34 |
| 3-Month (gavage) | C-89-0017-T | | | 36 |
| 1-Year (gavage) | I-93-0020-T | C-47320, C-47341, C-47342, R-47344, C-48351, R-48613 and C-48616 | DCT | 37 |
| Dog | | | | |
| 1-Month (I.V.) | C-88-0014-T | 06 | DPT | 41 |
| 1-Year (capsule) | I-92-0168-T | C-46711, C-47320, C-47342, C-47344, C-48351, C-48616 and R-48613 | DCT | 43 |
| Monkey | | | | |
| 1-Month (I.V.) | C-88-0015-T | 06 | DPT | 45 |
| 3-Month (gavage) | C-89-0020-T | 23 | DPT | 47 |

DPT = Department of Pathology and Toxicology
Merrell Dow Research Institute
Merrell Dow Pharmaceuticals, Inc.,
Cincinnati, Ohio

DCT = Department of Toxicology
Cincinnati Center
Marion Merrell Dow Inc.,
Kansas City, MO

DIC = Department of Drug Safety
Indianapolis Center
Marion Merrell Dow Inc.,
Kansas City, MO

HES = Health Environmental Sciences
The Dow Chemical Co.
Indianapolis, IN

HEST = Health Environmental Sciences
The Dow Chemical Co.
Freeport, TX

All the above mentioned studies were reviewed under NDA 20-623 (please see review dated July 5, 1996). Results of i.v. pharmacology and toxicology studies will be discussed here only.

Proposed Text of the Labeling for Anzemet:

The label is according to 21 CFR, 201.50, Subpart B (April 1, 1995). However, the following changes should be incorporated:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility:

Sponsor's Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dolasetron mesylate was not mutagenic in in vitro Ames assay, rat lymphocyte chromosomal aberration assay, chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase forward mutation assay, or rat hepatocyte UDS assay or in vivo in IV and oral mouse micronucleus assays. Dolasetron mesylate 2-year oral carcinogenicity studies were conducted in mice and rats. Dolasetron mesylate was not carcinogenic in rats at doses 83 and 167 times (based on mg/kg) the recommended human IV dose (1.8-mg/kg), in males and females, respectively. In mice, dolasetron mesylate was not carcinogenic at doses 42 times the recommended human IV dose. Liver tumors in males and endometrial polyps in females were found at 83 times the highest recommended human dose. Fertility and reproductive performance were not affected by oral administration of dolasetron mesylate to male and female rats at doses 222 and 56 times the highest recommended human dose, respectively.

Evaluation:

In 2-year carcinogenicity study in Crl:CD-1 (ICR) mice, MDL 73,147 was given via diet at daily doses of 75, 150 and 300 mg/kg/day. The highest tested dose is the maximum tolerated dose, since it produced histopathological changes in the target organ (liver) of toxicity. Hence, dose selection was appropriate. Treatment had no significant effect on inter-current mortality rates and survival rates at the end of study period were comparable in all groups. In males increased incidences of hepatocellular adenomas and hepatocellular carcinomas were seen. Increase in the incidences of hepatocellular adenomas reached to statistical significance only in one sex (males: $p = 0.0001$; Peto trend test). Pairwise comparison (Fisher exact test) of incidences of hepatocellular adenomas between control and individual treatment groups showed significance for mid and high dose treated males (p values: 0.0001 and 0.004 respectively). It should also be noted that incidence rate of hepatocellular adenoma in high dose treated male mice was within range of historical incidence rate (high dose [300 mg/kg/day] = 23.6%, published historical control

incidence rate = 18.6% . In males, increase in the incidences of hepatocellular carcinoma was not statistically significant (males: p = 0.0512; Peto trend test). If one adds the incidence of hepatocellular adenomas to the incidence of hepatocellular carcinomas then the combined incidence of any liver lesion (i.e. adenomas and/or carcinomas) become statistically significant in males (p = 0.0000; Peto trend test). Sponsor testing laboratory does not have historical control incidence rate, since this is the first time they have conducted 2-year carcinogenicity study in CD-1 mice. Data indicated that MDL 73,147 is tumorigenic in male mouse. The drug is not genotoxic, therefore it is non-genotoxic carcinogen. Sponsor has not investigated the non-genotoxic mechanisms of the production of liver tumors in treated male mouse. Furthermore, tumor (hepatocellular adenomas) seen in male mice is due to drug induced liver toxicities (centrolobular hypertrophy, single cell degeneration/necrosis and altered eosinophilic foci). Based on mg/sqm, high dose treated mice (300 mg/kg/day = 900 mg/sqm) were exposed to about 13.5 time higher than the recommended human dose (1.8 mg/kg = 66.6 mg/sqm, i.v.). Increase in hepatocellular adenomas in male mice were seen at ≥150 mg/kg/day, which on the basis of mg/sqm is about 6.7 time higher than the recommended human dose (1.8 mg/kg = 66.6 mg/sqm, i.v.). Next lower dose (75 mg/kg/day) can be considered as threshold dose for Dolasetron's carcinogenic effect.

In 2-year carcinogenicity study in Crl:CD(SD)BR rats, MDL 73,147 was given via diet at daily doses of 75, 150 and 300 mg/kg/day in males and 150, 300 and 600 mg/kg/day in females (it should be noted that MTD in 3-month dose ranging study was close to 250 mg/kg/day). More than 85% of high dose (300 mg/kg/day in males and 600 mg/kg/day in females) treated rats had hematuria, therefore, all rats in high dose group were killed and discarded on day 228/229 of the study. On day 176 of the study, sponsor added 4 additional groups (male control group, female control group, male treated with 25 mg/kg/day and female treated with 50 mg/kg/day) and dosed for 2-years (day 176 was designated as study day 1 for these groups). Hence, the selection of top dose in the initial experiment exceeded MTD. The new top doses (i.e. 150 mg/kg/day in males and 300 mg/kg/day in females) are close to MTD. Hence, dose selection was appropriate. Even though experiment was conducted in two "time period" i.e. one of the control group and low dose group were started on day 176 of the study and continued for full 2-years, overall conduct of the study is acceptable. In all the analysis, initial top doses (i.e. 300 mg/kg/day in males and 600 mg/kg/day in females) were excluded. For analysis purposes only doses 25, 75 and 150 mg/kg/day in males and 50, 150 and 300 mg/kg/day in females were used. The treatment had no significant effect on intercurrent mortality rates and survival rates at the end of treatment period were comparable in all groups. At the end of treatment period, final body weights in

males were 14%, 13% and 19% lower than control final body weight at low, mid and high dose respectively, and the corresponding values in females were 15%, 15% and 27% respectively. Based on mg/sqm, highest tested dose in males (150 mg/kg/day) and females (300 mg/kg/day) were 13.3 and 26.6 fold higher than the recommended daily dose in human (1.8 mg/kg = 66.6 mg/sq.m., i.v.) respectively. With respect to non-neoplastic findings, increased incidences of thymus involution and cystic glandular hyperplasia in the mammary gland were seen in high dose treated females. No treatment related neoplastic findings were evident in this study. Thus, MDL 73,147 did not show carcinogenic effect in 2-year carcinogenicity study in rats.

Anzemet was not mutagenic in Ames test, rat lymphocyte chromosomal aberration test, Chinese hamster ovary cell/HGPRT forward gene mutation assay, mouse bone marrow micronucleus test (oral and i.v.) and in vitro rat hepatocyte

**Proposed Version**:

In 104-week dietary carcinogenicity study, mice (Crl:CD-1 [ICR]) were treated orally with Anzemet 75, 150 and 300 mg/kg/day (225, 450 or 900 mg/sq.m./day). For a 50 kg person of average height (1.46 sq.m. body surface area), these doses represent 3.4, 6.7 and 13.5 times the recommended clinical dose (66.6 mg/sq.m., i.v.) on a body surface area basis. Increase in hepatocellular adenomas only in male mice were seen at ≥150 mg/kg/day, which on the basis of mg/sqm is about 6.7 time higher than the recommended human dose (1.8 mg/kg = 66.6 mg/sqm, i.v.). The drug is not genotoxic, therefore it is non-genotoxic carcinogen. Next lower dose (75 mg/kg/day) can be considered as threshold dose for Dolasetron's carcinogenic effect.

In 104-week dietary carcinogenicity study, male rats (SD) were treated orally with Anzemet 25, 75, 150 mg/kg/day while females were treated with 50, 150 and 300 mg/kg/day (147.5, 442.5 and 885 mg/sq.m./day in males and 295, 885 and 1770 mg/sq.m./day). For a 50 kg person of average height (1.46 sq.m. body surface area), these doses represent 2.2, 6.6 and 13.3 times the recommended clinical dose (66.6 mg/sq.m., i.v.) on a body surface area basis in males and the corresponding ratio in females were 4.4, 13.3 and 26.6 respectively. Anzemet did not show carcinogenic effect in 104-week carcinogenicity study in rats.

Anzemet was not mutagenic in Ames test, rat lymphocyte chromosomal aberration test, Chinese hamster ovary cell/HGPRT forward gene mutation assay, mouse bone marrow micronucleus test (oral and i.v.) and in vitro rat hepatocyte unscheduled DNA synthesis (UDS) assay.

Anzemet at oral doses up to 400 mg/kg/day (2360 mg/sq.m./day, 35.4 times the recommended human i.v. dose based on body surface area) was found to have no effect on the fertility and reproductive performance of male rats. Anzemet at oral doses up to 100 mg/kg/day (590 mg/sq.m./day, 8.8 times the recommended human i.v. dose based on body surface area) was found to have no effect on the fertility and reproductive performance of female rats.

2. Pregnancy:

Sponsor's Version:

**Teratogenic Effects. Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses up to 33 and 11 times, respectively, the human dose (1.8 mg/kg) 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.

**Nonteratogenic Effects.** No embryofetal effects were observed in rats or rabbits following intravenous doses 33 and 11 times the human dose (1.8 mg/kg), respectively. Slight (6% and 13%) reductions in fetal weights at oral dolasetron mesylate doses 56 times the recommended human dose were observed in rats and rabbits. In rabbits, oral doses 11 times the recommended human dose resulted in early resorptions and postimplantation losses.

Evaluation:

The text is not according to 21 CFR, 201.50, Subpart B (April 1, 1995).

Proposed Version:

**Pregnancy: Teratogenic Effects. Pregnancy Category B.**

Reproduction studies have been performed in rats (up to 60 mg/kg/day) and rabbits (up to 20 mg/kg/day) at i.v. doses up to 33 and 11 times the human dose (1.8 mg/kg/day = 66.6 mg/sq.m.; 50 kg body weight assumed) on the basis of mg/kg/day and up to 5.3 and 2.6 times the human dose on the basis of mg/sq.m. respectively which revealed no evidence of impaired fertility or harm to the fetus due to Anzemet. 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.

3. Overdosage:

Sponsor's Version:

A 7-year-old male received 6 mg/kg orally before surgery. No symptoms occurred and no treatment was required.

It is not known if dolasetron is removed by hemodialysis or peritoneal dialysis.

Following a suspected overdose of ANZEMET, a patient found to have second-degree or higher AV conduction block should undergo cardiac telemetry monitoring.

There is no known specific antidote for dolasetron mesylate, and patients with suspected overdose should be managed with supportive therapy. Individual doses as large as 5 mg/kg intravenously or 400 mg orally have been safely given to healthy volunteers or cancer patients.

Evaluation:

Sponsor did not provide any clinical or preclinical overdose data. Acute i.v. toxicity of Dolasetron mesylate was studied in mice and rats. The minimum i.v. lethal doses were 160 mg/kg for male mice and 140 mg/kg for female mice and rats of both sexes. Clinical signs in both species were tremors, depression and convulsions.

Proposed Version:

The following sentences should be added to the sponsor's version:

The minimum i.v. lethal doses were 160 mg/kg for male mice and 140 mg/kg for female mice and rats of both sexes. Clinical signs in both species were tremors, depression and convulsions.

**SUMMARY AND EVALUATION:**

Dolasetron is a selective $5HT_3$ receptor antagonist. It does not have any significant dopamine antagonist activity, thus void of any significant extrapyramidal side effects. Intravenous administration of dolasetron significantly reduced the number of cisplatin-induced vomiting and delayed the onset of the first vomiting in ferrets (0.5 mg/kg, b.i.d.) and dogs (0.1 mg/kg). Antiemetic effect of dolasetron in dogs were similar to that seen with other $5HT_3$ antagonists (tropisetron, ondansetron and zacopride).

In support of the new drug application for dolasetron (injection), sponsor has referred to their NDA 20-623 (dolasetron tablets). I have consulted NDA 20-623 review (date of review: 7/5/96) for my summary and evaluation. Only results of i.v. pharmacology and i.v. toxicology studies (acute toxicity studies in mice, rats, dogs and monkeys; 1-month i.v. toxicity studies in rats, dogs and monkeys; i.v. Segment II. teratology studies in rats and rabbits) will be discussed here.

In anesthetized dogs, intravenous dose of 1 mg/kg of MDL 73,147EF had no effect on heart rate, blood pressure or ECG. However, 2 - 4 mg/kg (i.v.) dose produced transient (<90 sec) reduction in blood pressure without affecting heart rate. In another experiment a cumulative dose of 6 mg/kg had no significant effect on hemodynamic parameters (heart rate, left ventricular BP, dP/dt max, systemic BP, end diastolic BP and heart rate) and cardiac conduction (PQ and RR intervals). However, a cumulative dose of 18.5 mg/kg and higher dose levels start affecting cardiac hemodynamic (decreased left ventricular BP, dP/dt max, systemic BP and heart rate) and cardiac conduction (significantly increased PQ and RR intervals).

In conscious dogs, a cumulative i.v. dose of 1 mg/kg of MDL 73,147EF had no effect on heart rate, blood pressure or ECG. However, significantly increased PR intervals were seen at i.v. cumulative doses of 3 to 30 mg/kg of MDL 73,147EF (PR interval: vehicle control = 90 ± 5 m sec, 3 mg/kg = 99 ± 6 m sec, 10 mg/kg = 107 ± 6 m sec and 30 mg/kg = 137 ± 7 m sec). The base line value for PR interval in beagle dogs is 94 ± 6 m sec. Therefore, only at cumulative dose of 30 mg/kg of dolasetron value of PR interval was out side the normal range and is approaching first degree heart block. In this experiment cumulative dose of 15 mg/kg ondansetron significantly decreased PR interval by 10 m sec. A cumulative i.v. dose of 10 mg/kg of MDL 73,147EF or 7 mg/kg of ondansetron had no significant effect on QTc interval in conscious dogs. However, at cumulative dose of 30 mg/kg of MDL 73,147EF QTc interval was also increased significantly (vehicle control = 291 ± 11 m sec, 30 mg/kg + 338 ± 11 m sec). A cumulative dose of 15 mg/kg of ondansetron also significantly increased QTc interval in conscious dogs (vehicle control = 281 ± 10 m sec 15 mg/kg = 316 ± 16 m sec).

In dogs (anesthetized or conscious), the no effect i.v. dose for cardiac toxicity is 1 mg/kg (see above) which is 10 times higher than the pharmacologically effective dose in dogs (ED85 = 0.1 mg/kg). Furthermore, a cumulative i.v. dose of 10 mg/kg in conscious dogs, which is about 5 times higher than the recommended human dose (1.8 mg/kg, i.v.), produced slight reversible increase in PR interval without affecting QTc interval (see above).

MDL 74,156 (the main metabolite of MDL 73,147) is also pharmacologically active (anti-emetic in ferrets, inhibition of Bezold-Jarisch Reflex in anesthetized rats, in vitro binds to $5\text{-}HT_3$ receptors). Sponsor did not report ED50 values for the drug or its main metabolite (MDL 74,156).

Dolasetron did not affect the antitumor activity of Cisplatin in three different tumor models (murine L1210 leukemia, ADJ/PC6 plasmacytoma and HX/110 human ovarian tumor xenograft models). Dolasetron also did not affect the antitumor activities of adriamycin, 5-fluorouracil and cyclophosphamide in two different tumor models (L1210 leukemia model in male mice and MDA-MB-231 human breast carcinoma xenograft model in female nude mice).

ADME studies have been conducted in rats, dogs, rabbits and monkeys. Irrespective of species and route of administration (i.v. or oral) the plasma $t_{½}$ of MDL 73,147 was close to 0.5 hr (human: not determined) and plasma $t_{½}$ of MDL 74,156 (major metabolite) was about 5 hr

Irrespective of species and route of administration (i.v. or oral), drug is metabolized rapidly. No parent drug was seen in urine or feces. MDL 74,156 is the main metabolite (it is also pharmacologically active) and the other metabolites were N-oxide, 5'-OH, 6'-OH and 7'-OH derivatives of MDL 74,156 and their corresponding conjugates.

Irrespective of species and route (i.v. or oral) of administration about % and of radioactivity were excreted in urine and feces (mainly biliary), and most of the excretion occurred during the first 48 hr period.

In vitro about 75 - 90% of the drug (MDL 73,147) was bound to rat, dog, monkey and human plasma, while binding of MDL 74,156 ranged 54 - 73% in all 4 species. In rat, MDL 73,147 is not a hepatic enzyme inducer.

In acute toxicity study, the minimum i.v. lethal doses were 160 mg/kg for male mice, 140 mg/kg for female mice and rats of both sexes. The highest nonlethal i.v. dose in female mice and rats of both sexes was 126 mg/kg. The highest nonlethal i.v. dose in male mice was 140 mg/kg. Clinical signs in both species were tremors, depression and convulsions at high doses. In dogs i.v. minimum lethal doses could not be determined since no animal died during the study period. However in dogs, higher doses (6-30 mg/kg i.v.) produced emesis and salivation lacrimation, tremors, chewing movements and panting. These clinical signs regress within 3.5 hours after dosing.

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."



/S/
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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17 Page(s) Redacted

DRAFT LABELING

STATISTICAL REVIEW AND EVALUATION --- NDA
(ADDENDUM)

Date:
JUL 28 1997

NDA #: 20-623, 20-624

Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet (Dolasetron mesylate) Tablet
Anzemet (Dolasetron mesylate) Injection

Indication: Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy, Including Initial and Repeat courses.
Prevention of PONV (Postoperative Nausea and Vomiting)
Treatment of PONV (Postoperative Nausea and Vomiting)

Documents Reviewed: NDA Suppl. dated June 6, 1997

Medical Reviewer: This review has been discussed with the medical Officer, Hugo Gallo-Torres, M.D., Ph.D.

Key Words: Pooling studies

A. Background

Reviewer's evaluation and comments on sponsor's results of pooling data from dolasetron controlled clinical trials were given in the statistical review and evaluation dated July 16, 1997.

Per request, for iv dolasetron for the prevention of PONV, this reviewer re-analyzed the proportion of complete responder from the pooled data which included studies MCPR0084 and 73147-2-S-080 and females in study MCPR0045.

For oral dolasetron for the prevention of CONV, the dose response profile for the pooled data and for individual dose response trials are attached as figures 1a and 1b.

B. Reviewer's Evaluation and Comments

1. Intravenous Dolasetron for the Prevention of PONV

If studies MCPR0084, 73147-2-S-080 and MCPR0045 were pooled for females, the estimate differences and 95% confidence intervals for the differences in the proportion of complete responders for

all comparisons are:

**IV Dolasetron for the Prevention of PONV --- Studies MCPR0045, MCPR0084 and 73147-2-S-080 for Females**
**Comparison of 12.5 mg and Higher Active Dose Groups**
**Difference in Proportions (Dose Group - 12.5 mg)**

| Dose Comparison | Estimate | 95% Conf. Interval |
|---|---|---|
| 12.5 mg vs. 25 mg | -0.02% | (-7.8%, 7.4%) |
| 12.5 mg vs. 50 mg | 0.02% | (-7.4%, 7.8%) |
| 12.5 mg vs. 100 mg | 4.0% | (-4.6%, 13.1%) |

Estimates and 95% confidence intervals were obtained using Exact method.

As seen in the above table, the analysis of proportion of complete responder from the pooled data for females shows that there were no differences among 12.5 mg, 25 mg and 50 mg. Therefore, 12.5 mg seems to be the minimal effective dose with maximum response in the pooled analysis for females.

**2. Oral Dolasetron for the Prevention of CCNV**

The dose response profile for the pooled data and for individual dose response trials are given in Figures 1a and 1b, respectively.

The statistical review and evaluation dated May 20, 1996 stated "antiemetic efficacy of dolasetron for prevention of CCNV was linear related to dose. The maximal effectiveness seems to be achieved with a single dose of 200 mg."

**C. Overall Summary and Recommendation**



**1. Intravenous Dolasetron for the Prevention of PONV**

The analysis of proportion of complete responder from the pooled data for females shows that there were no differences among 12.5 mg, 25 mg and 50 mg. Therefore, 12.5 mg seems to be the minimal effective dose with maximum response in the pooled analysis for females.

**2. Oral Dolasetron for the Prevention of CCNV**

The maximal effectiveness seems to be achieved with a single dose of 200 mg.

/S/

/Milton C. Fan, Ph.D.
Mathematical Statistician

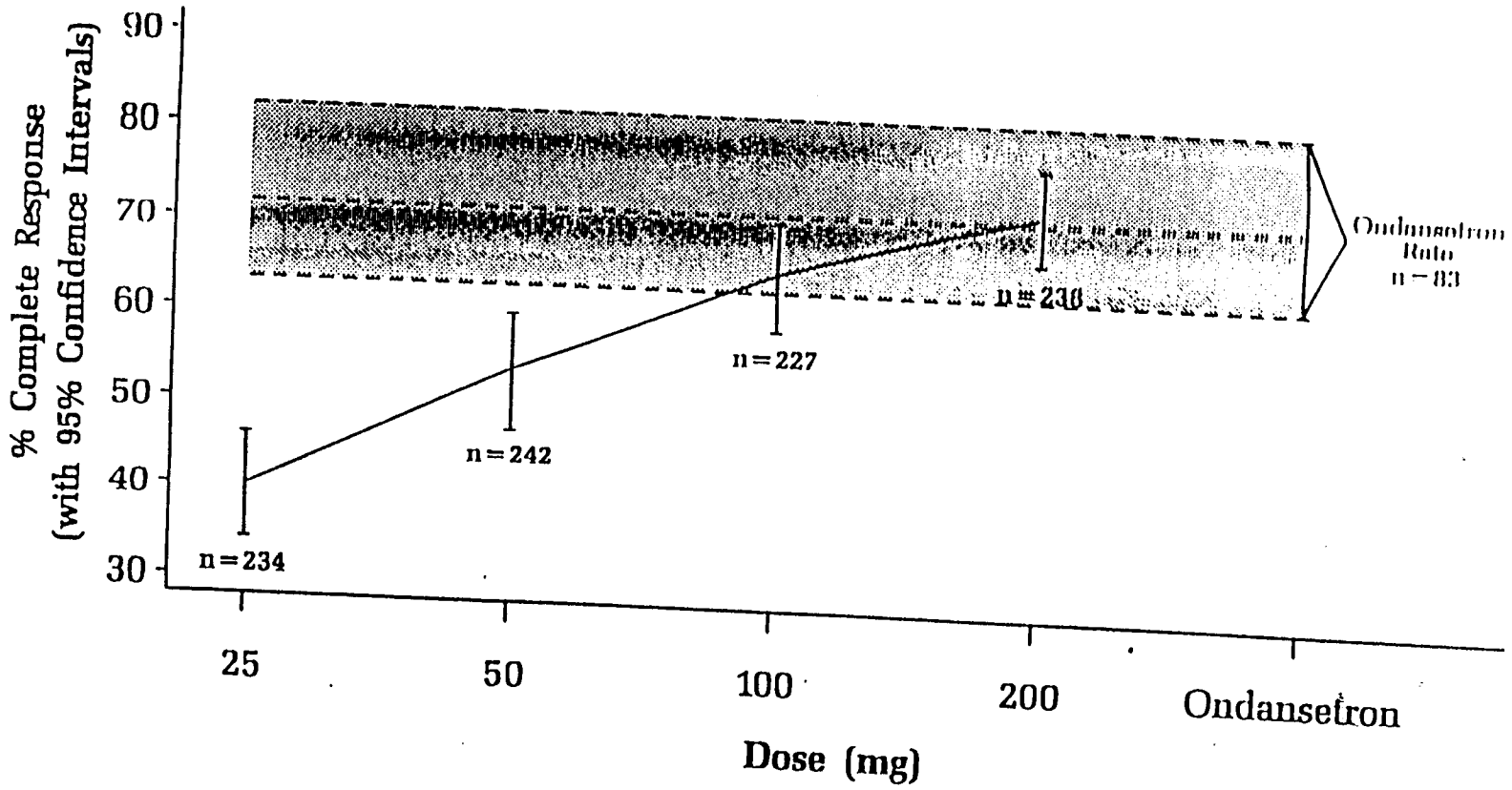
This review consists of 3 pages of text and 2 pages of tables.

Concur: Dr. Huque /S/ 7/22/97
Dr. Smith /S/ 7/28/97

cc:
Archival NDA 20-623, 20-624
HFD-180
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. Copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/07/22/97

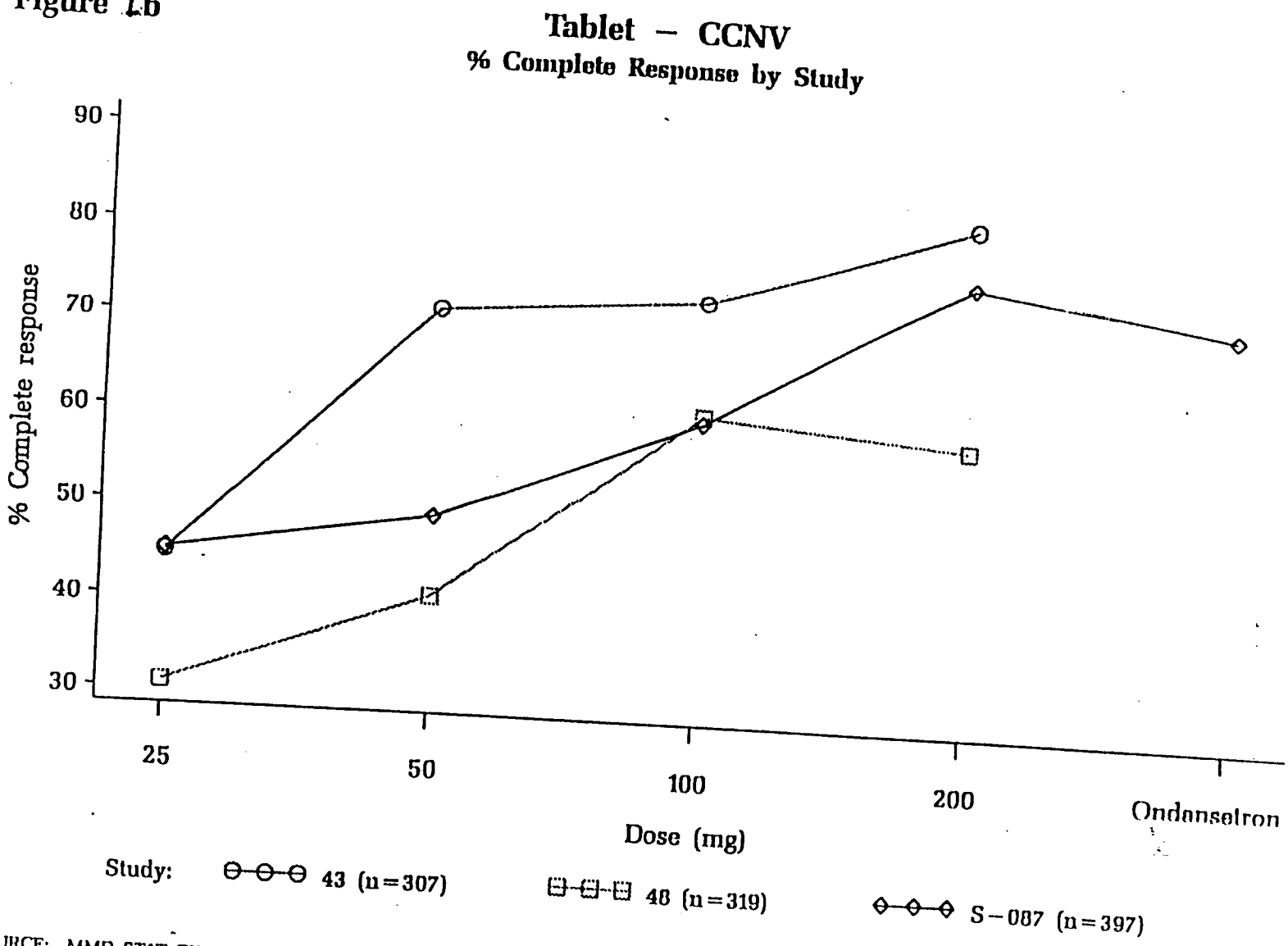
Figure 1a

**Oral Dolasetron/Chemotherapy**
**Randomized, Double Blind Trials**
**Complete Response by Dose**
**(Linear dose response, p<.0001)**
**(200 vs 25, p<.0001)**




Includes studies MCPR0043, MCPR0048, 2-S-087
Source: MMD NM00274 - DOLCHEMO.SAS - (04JUN97, 16:04)

Figure 1b




SOURCE: MMD STAT_CDM NM08274 -OCHEM_EFF_4.SAS- (05JUN07, 16:05)

STATISTICAL REVIEW AND EVALUATION --- NDA

Date: JUL 16 1997

NDA #: 20-623, 20-624

Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet(Dolasetron mesylate) Tablet
Anzemet(Dolasetron mesylate) Injection

Indication: Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy, Including Initial and Repeat Courses.
Prevention of PONV (Postoperative Nausea and Vomiting)
Treatment of PONV (Postoperative Nausea and Vomiting)

Documents Reviewed: NDA Suppl. dated June 6, 1997

Medical Reviewer: This review has been discussed with the medical officer, Hugo Gallo-Torres, M.D., Ph.D.

Key Words: Pooling studies, logistic regression

A. Background

The sponsor formally submitted this NDA supplemental to document results of pooling of data from Dolasetron controlled clinical trials.

This document outlines the justification for pooling the efficacy data from pivotal dose response trials of dolasetron that were presented in the Integrated Summary of Efficacy (ISE) for the original NDA. This document describes data analytic approaches for analyzing the pooled data for each indication for which the sponsor and FDA currently having differing dose recommendations. Those indications are:

- * intravenous dolasetron for treatment and prevention of PONV
- * oral dolasetron for prevention of PONV, and
- * oral dolasetron for prevention of CCNV.

Some of rationales for FDA dose recommendations were given in the

statistical review and evaluation dated May 20, 1996, Jan 17, 1997, respectively for the above 3 indications.

For oral dolasetron for the prevention of CCNV, the statistical review and evaluation dated May 20, 1996 stated "antiemetic efficacy of dolasetron mesylate tablets in prevention of CCNV was linear related to dose. The maximal effectiveness seems to be achieved with a single dose of 200 mg."

This review will not discuss the issues of dose selection for the indications of oral dolasetron for prevention of CCNV. Instead, this review will discuss mainly the issues of dose selection for the indications of 1) oral dolasetron for prevention of PONV, and 2) intravenous dolasetron for treatment and prevention of PONV.

**B. Sponsor's Analysis**

**1. Pooling Data for Dosage Selection**

**a). Clinical and Scientific Rationale**

There were two considerations about pooling of data from independent studies. First, one must assess whether studies are sufficiently compatible to permit pooling of data. Issues regarding study design, patient population, dosing regiments, duration of follow-up etc must be reviewed to answer this question. Second, if the decision is made that studies are suitable for pooling, then one must decide how the pooling will be done, i.e., what statistical methodology is useful for answering the questions at hand.

In the case of the dolasetron program, the primary interest is to characterize the dose response profile in order to select the optimal dose of dolasetron in each indication. The sponsor's intent was to select the minimum dose with the maximal effect, i.e., the lowest dose on the plateau of the dose response curve.

The sponsor's intent for pooling of data was considered prospectively by the consistency of individual study designs and the multiple dose response studies that were conducted for each indication. The Phase III programs for the various indications were designed by a common Global Project Team. While slight variations were allowed to meet some regional needs or

accommodate the distinct indications, the essential elements of trial design and conduct were the same across all studies. Some of those major elements are:

all studies use a placebo, active control or low dose control;
inclusion/exclusion criteria were harmonized across studies;
medical procedures were similar;
the primary response variable were identically defined;
a common 24-hour evaluation window was used.

In addition to these design elements, studies were done concurrently in time to minimize potential bias due to changing medical practice over time. As noted in the sponsor's clinical study report, patients characteristics, medical histories and important prognostic factors were well-balanced across control and dose groups.

In order to increase the precision of the overall estimates of the dose effect, the sponsor believes that the data from these studies are appropriate for pooling.

b). Statistical Consideration

The definite dose response studies in the ISE were evaluated using a separate logistic regression analysis for each indication. For the present analysis, the model included a study identifier, dose group and a term for study-by-dose group interaction. The interaction term was used to assess the parallelism of the dose response curves across studies. The model may be written as:

logit=study dosegroup study*dosegroup

The outcomes of the tests for parallelism from the logistic model were summarized below.

Assessing Parallelism of Dose Response Across Studies Using Logistic Regression

| Indication | Number of Studies | Logistic Regression Study*dose Group Interaction P-value |
|---|---|---|
| IV PONV Treatment | 2 | 0.3859 |
| IV PONV Prevention | 3 | 0.4103 |
| Oral PONV Prevention | 2 | 0.2350 |

Copied from Table 1, page 4 of NDA supplemental dated 6/6/97.

Each of these p-values is large enough to indicate that the dose response profiles are parallel across the dose studies. In considering the power of these tests to detect meaningful differences in the parallelism of the dose response profiles. It is difficult to define an alternative hypothesis of interest since there are many patterns of dose response that could be evaluated. However, these p-values are sufficient large and are based on 2 or 3 studies each involving 300 to 1000 patients for each indication.

Estimation of the dose effect and the difference between selected doses is of interest for the pooled data. At the request of FDA Biometric Division, exact estimation of the odds ratio and confidence intervals (Mantel-Haenzsel test) was used since it is not model dependent as is the case of logistic regression. Also, exact estimates of the odds ratio and confidence intervals were computed for the difference in proportions. To assess the consistency of the results, the logistic regression model given above without the interaction term was used to estimate the odds ratio and its confidence intervals.

For the dolasetron injections (treatment and prevention) for PONV, the dose comparisons of greatest interest were:

12.5 mg versus 25 mg
12.5 mg versus 50 mg, and
12.5 mg versus 100 mg.

Small differences between the proportion of responders with narrow confidence intervals indicates similarity of response

across this broad dose range (i.e. 12.5 mg to 100 mg) and the existence of a dose response plateau beginning at 12.5 mg.

For the oral dolasetron indications for the prevention of PONV, the dose comparisons of greatest interest were

50 mg versus 100 mg, and
50 mg versus 200 mg.

Again, small differences between the proportion of responders with narrow confidence intervals indicate a dose response plateau at the 50 mg oral dose.

**2. Intravenous Dolasetron for the Treatment of PONV**

The dose response profile for the pooled data and for individual dose response trials are given in Figures 1a and 1b, respectively.

The estimated differences and 95% confidence intervals for the differences in the proportion of complete responders for all comparisons are given below.

**IV Dolasetron for the Treatment of PONV--- Pooled**
**Comparison of 12.5 mg and Higher Active Dose Groups**
**Difference in Proportions (Dose Group - 12.5 mg)**

| Dose Comparison | Estimate | 95% Conf. Interval |
|---|---|---|
| 12.5 mg vs. 25 mg | -3.9% | (-14.1%, 5.9%) |
| 12.5 mg vs. 50 mg | 0.3% | (-9.5%, 10.5%) |
| 12.5 mg vs. 100 mg | -3.8% | (-14.1%, 5.7%) |

Estimates and 95% confidence intervals were obtained using Exact method.
Copied from Table 2, page 7, NDA Supplemental dated 6/6/97.

**3. Intravenous Dolasetron for the Prevention of PONV**

The dose response profile for the pooled data and for individual dose response trials are given in Figures 2a and 2b, respectively.

The estimated differences and 95% confidence intervals for the

differences in the proportion of complete responders for all comparisons are given below.

**IV Dolasetron for the Prevention of PONV--- Pooled Comparison of 12.5 mg and Higher Active Dose Groups Difference in Proportions (Dose Group - 12.5 mg)**

| Dose Comparison | Estimate | 95% Conf. Interval |
|---|---|---|
| 12.5 mg vs. 25 mg | -0.1% | (-7.3%, 6.7%) |
| 12.5 mg vs. 50 mg | 1.9% | (-5.0%, 8.9%) |
| 12.5 mg vs. 100 mg | 3.1% | (-4.7%, 11.1%) |

Estimates and 95% confidence intervals were obtained using Exact method.
Copied from Table 3, page 11, NDA Supplemental dated 6/6/97.

4. Oral Dolasetron for the Prevention of PONV

The dose response profile for the pooled data and for individual dose response trials are given in Figures 3a and 3b, respectively.

The estimated differences and 95% confidence intervals for the differences in the proportion of complete responders for all comparisons are given below.

**Oral Dolasetron for the Prevention of PONV--- Pooled Comparison of 50 mg and Higher Active Dose Groups Difference in Proportions (Dose Group - 50 mg)**

| Dose Comparison | Estimate | 95% Conf. Interval |
|---|---|---|
| 50 mg vs. 100 mg | -0.1% | (-7.3%, 6.7%) |
| 50 mg vs. 200 mg | 1.9% | (-5.0%, 8.9%) |

Estimates and 95% confidence intervals were obtained using Exact method.
Copied from Table 3, page 11, NDA Supplemental dated 6/6/97.

C. Reviewer's Evaluation and Comments

In all these studies, there is not enough power to detect the differences among dose groups (e.g. oral 50 mg vs. 100 mg for prevention of PONV and intravenous 12.5 mg vs. 25 mg for treatment and prevention of PONV) due to insufficient sample

size.

Sponsor's additional analyses are post-hoc and exploratory analyses and hypothesis generating. Efficacy of test drug should be mainly based on the results from individual study not from the results of pooling studies.

1. **Pooling Data for Dosage Selection**

a). **Reviewer's Comments on Sponsor's Clinical and Scientific Rationale**

For each indication, there were one or two U.S. studies and one European study conducted. The protocols used in these studies were not identical. These studies were not designed to be pooled. In general, these studies are not sufficiently compatible in terms of sample size determination, patient population, inclusion and exclusion criteria, and concurrent medications.

For IV PONV prevention, the sponsor included three clinical trials (MCPR0084, MCPR0045 and 73147-2-S-80). Both studies MCPR0084 and 73147-2-S-80 included only female patients. Studies MCPR0045 included both male and female patients. Statistically significant gender by treatment interaction was observed in Study MCPR0045. So, the study population for study MCPR0045 was different from those for other two studies. Because of this reason, the study MCPR0045 should be not pooled with the other two studies.

If one intends to pool studies, one should consider only to pool studies MCPR0084 and 73147-2-S-80.

b). **Reviewer's Comments on Sponsor's Statistical Consideration**

The sponsor evaluated definite dose response studies in the ISE using a separate logistic regression analysis for each indication. For the analysis, the model included a study identifier, dose group and a term for study-by-dose group interaction. The interaction term was used to assess the parallelism of the dose response curves across studies.

The power of testing study-by-dose group interaction is very low. The significance level of 0.25 is highly recommended (see pages

86 and 108, Hosmer, D. W. and Lemeshow, S. (1989) "Applied Logistic Regression"). P-values for IV PONV treatment and IV PONV prevention seems large enough to indicate that the dose response profiles are parallel across the dose studies. However, p-values for the oral PONV prevention might be not sufficient large to indicate that the dose response profiles are parallel across the dose studies.

2. Intravenous Dolasetron for the Treatment of PONV

As seen in Figure 1b, the dose response profile for individual dose response trials shows as following:

1) Study MCPR0044 showed 12.5 mg is the minimal dose with maximum response.

2) Study 73147-2-S-0084 showed 12.5 mg and 25 mg results are about the same with a slightly numerical advantage for the 25 mg.

The p-value for interaction between dose and study in the pooled analysis was large enough ($p>0.25$) to indicate that the dose response profiles are parallel across the dose studies.

In the view of 95% confidence interval for the difference in the proportion of complete responders for comparisons between 25 mg and 12.5 mg in the pooled analysis, it indicates that the confidence interval (-14.1%, 5.9%) was not symmetric and the lower limit is lower than 10.0%. In the worst case, 25 mg would be inferior to 12.5 mg by 14.1%. So, 12.5 mg seems to be minimal effective dose with maximum response in the pooled analysis.

3. Intravenous Dolasetron for the Prevention of PONV

As seen in Figure 2b, the dose response profile for for individual dose response trials showed that dose response curves were different and reached the plateau at 12.5 mg and 25 mg, respectively for study MCPR0084 and study 73147-2-S-80.

As stated in Section C.1.a), the study population for study MCPR0045 was different from those for other two studies (MCPR0084 and 73147-2-S-080). The study MCPR0045 should be not pooled with the other two studies.

If studies MCPR0084 and 73147-2-S-080 were pooled, the estimated differences and 95% confidence intervals for the differences in the proportion of complete responders for all comparisons are:

**IV Dolasetron for the Prevention of PONV --- Studies MCPR0084 and 73147-2-S-080**
**Comparison of 12.5 mg and Higher Active Dose Groups**
**Difference in Proportions (Dose Group - 12.5 mg)**

| Dose Comparison | Estimate | 95% Conf. Interval |
|---|---|---|
| 12.5 mg vs. 25 mg | 4.6% | (-5.1%, 14.6%) |
| 12.5 mg vs. 50 mg | 5.3% | (-4.4%, 15.3%) |
| 12.5 mg vs. 100 mg | 8.2% | (-6.4%, 24.1%) |

Estimates and 95% confidence intervals were obtained using Exact method.

As seen in the above table, all of upper confidence limits are large in magnitude, so there is therapeutic gain by using the higher dose (e.g. 25 mg).

In the view of 95% confidence interval for the difference in the proportion of complete responders for comparisons between 25 mg and 12.5 mg in the pooled analysis, it indicates that the confidence interval (-5.1%, 14.6%) was not symmetric and the upper limit is higher than 10.0% in favor of the 25 mg dose. Therefore, 25 mg seems to be the minimal effective dose with maximum response in the pooled analysis.

Furthermore, as stated in the Statistical Review and Evaluation for the prevention of PONV for IV Dolasetron dated January 17,

"Two studies (MCPR0084 and 73147-2-S-80) showed that there was a significant overall effect for the "complete response" endpoint. For this endpoint, the highest observed complete response rates were achieved for the 50 mg dose in Study MCPR0084 and for the 25 mg dose in Study 73147-2-S-80.

Study MCPR0084 showed the 12.5 mg, 25 mg, and 50 mg dose groups were statistically significantly more effective than placebo. Study 73147-2-S-80 showed that only 25 mg dose group was statistically significantly better than the placebo."

Furthermore, study MCPR0045 showed that the linear dose trend was not significant.

Hence, the 25 mg comes out to be the optimal effective dose which was supported by both studies (MCPR0084 and 73147-2-S-080).

4. Oral Dolasetron for the Prevention of PONV

As seen in Figure 3b, the dose response profile for individual dose response trials showed that dose response curves were different and reached the plateau at 50 mg and 100 mg, respectively for study 73147-2-S-095 and study AN-PO-0292.

The p-value for interaction between dose and study in the pooled analysis was not sufficient large enough ($p<0.25$) to indicate that the dose response profiles are parallel across the dose studies. Hence, pooling of two studies is statistically not convincing.

Furthermore, all two studies (AN-PO-0292 and 73147-2-S-095) had highly significant trend with dose. Both studies showed that the 100 mg was significantly more effectively than placebo. But only study 73147-2-S-095 showed that the 50 mg was significantly more effectively than placebo.

In the comparison between 50 mg and 100 mg, there was a numerical difference of about 13% in favor of 100 mg group in complete response in the study AN-PO-0292. But, in the study 73147-2-S-095, there is a slight difference of about 6% in favor of 50 mg group in complete response.

Hence, the 100 mg seems to be the optimal effective dose which was supported by both studies (AN-PO-0292 and 73147-2-S-095).

D. Overall Summary and Recommendation

1. Pooling Data for Dosage Selection

Sponsor's additional analyses are post-hoc and exploratory analyses. Efficacy of test drug should be mainly based on the results from individual study not from the results of pooling studies.

P-values of study-by-dose group interaction for IV PONV treatment and IV PONV prevention seem large enough to indicate that the dose response profiles are parallel across the dose studies. However, p-values for oral PONV prevention might not not sufficient large enough to indicate that the dose response profiles are parallel across the studies.

For IV PONV prevention, both studies MCPR0084 and 73147-2-S-80 included only female patients. Studies MCPR0045 included both male and female patients. Statistically significant gender by treatment interaction was observed in Study MCPR0045. So, the study population for study MCPR0045 was different from those for other two studies. Therefore, the study MCPR0045 should be not pooled with the other two studies.

**2. Intravenous Dolasetron for the Treatment of PONV**

Study MCPR0044 showed 12.5 mg is the minimal dose with maximum response. Study 73147-2-S-0084 showed 12.5 mg and 25 mg results are about the same with a slightly numerical advantage for the 25 mg.

The 95% confidence interval (for the difference in the proportion of complete responders for comparisons between 25 mg and 12.5 mg in the pooled analysis) indicates that the confidence interval of (-14.1%, 5.9%) was not symmetric and the lower limit is lower than 10.0%. In the worst case, 25 mg would be inferior to 12.5 mg by 14.1%. Therefore, 12.5 mg seems to be minimal effective dose with maximum response in the pooled analysis.

**3. Intravenous Dolasetron for the Prevention of PONV**

The 25 mg is recommended as the optimal effective dose which was supported by both studies (MCPR0084 and 73147-2-S-080).

**4. Oral Dolasetron for the Prevention of PONV**

The 100 mg is recommended as the optimal effective dose which was supported by both studies (AN-PO-0292 and 73147-2-S-095).

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

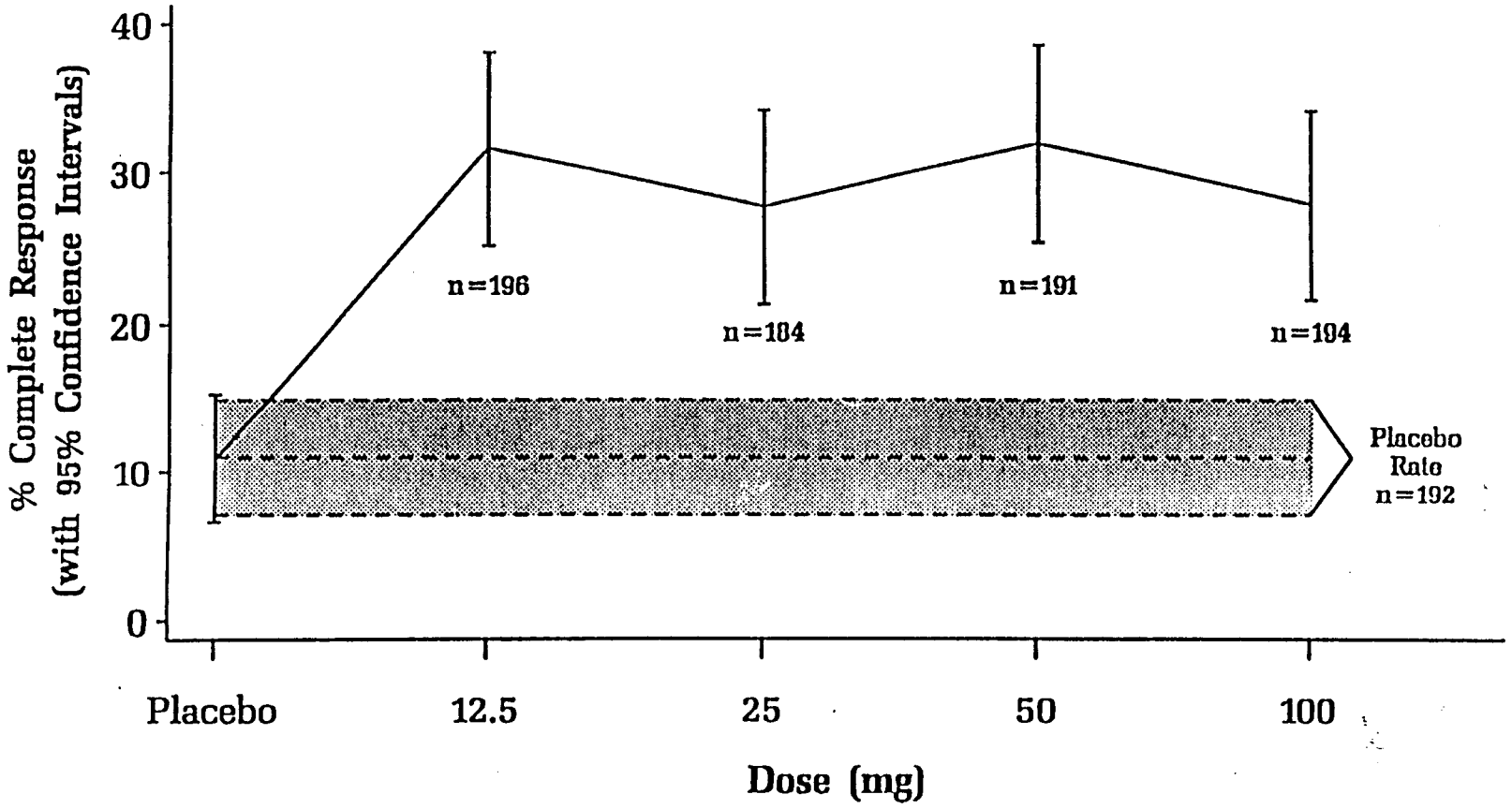
This review consists of 12 pages of text and 6 pages of tables.

concur: Dr. Huque /S/ 1/8/97
Dr. Smith /S/ 1/15/97

cc:
Archival NDA 20-623, 20-624
HFD-180
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. Copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/07/08/97

Figure 1a

# IV Dolasetron/PONV (Treatment)
## Randomized, Double Blind Trials
### Complete Response by Dose
(12.5 vs Placebo, P<.0001)



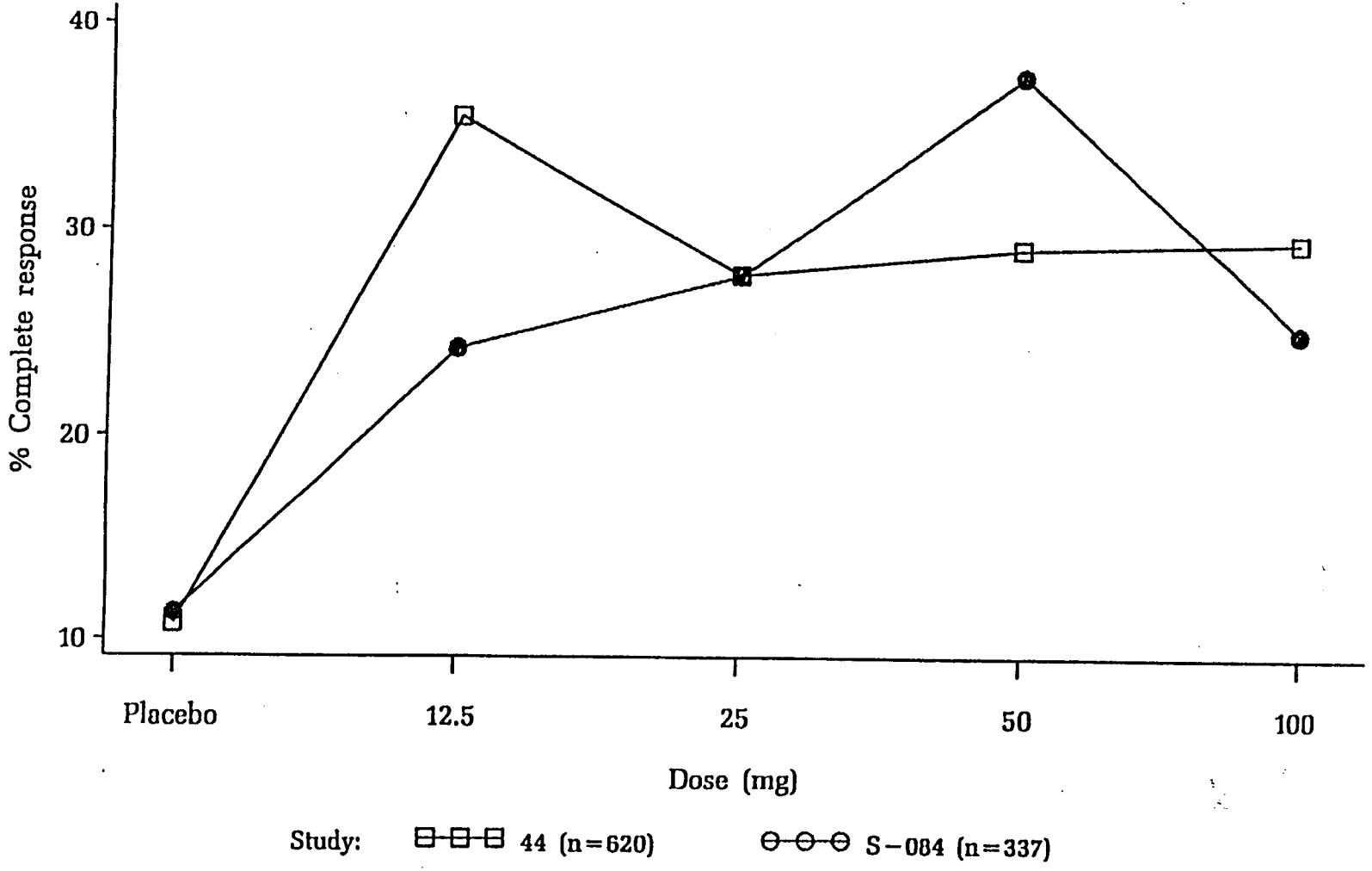

Includes studies MCPR0044, 73147-2-S-084

tce: MMD NM08274 - IVPONV.SAS - (04JUN97, 16:20)

Figure 1b

# IV PONV Treatment

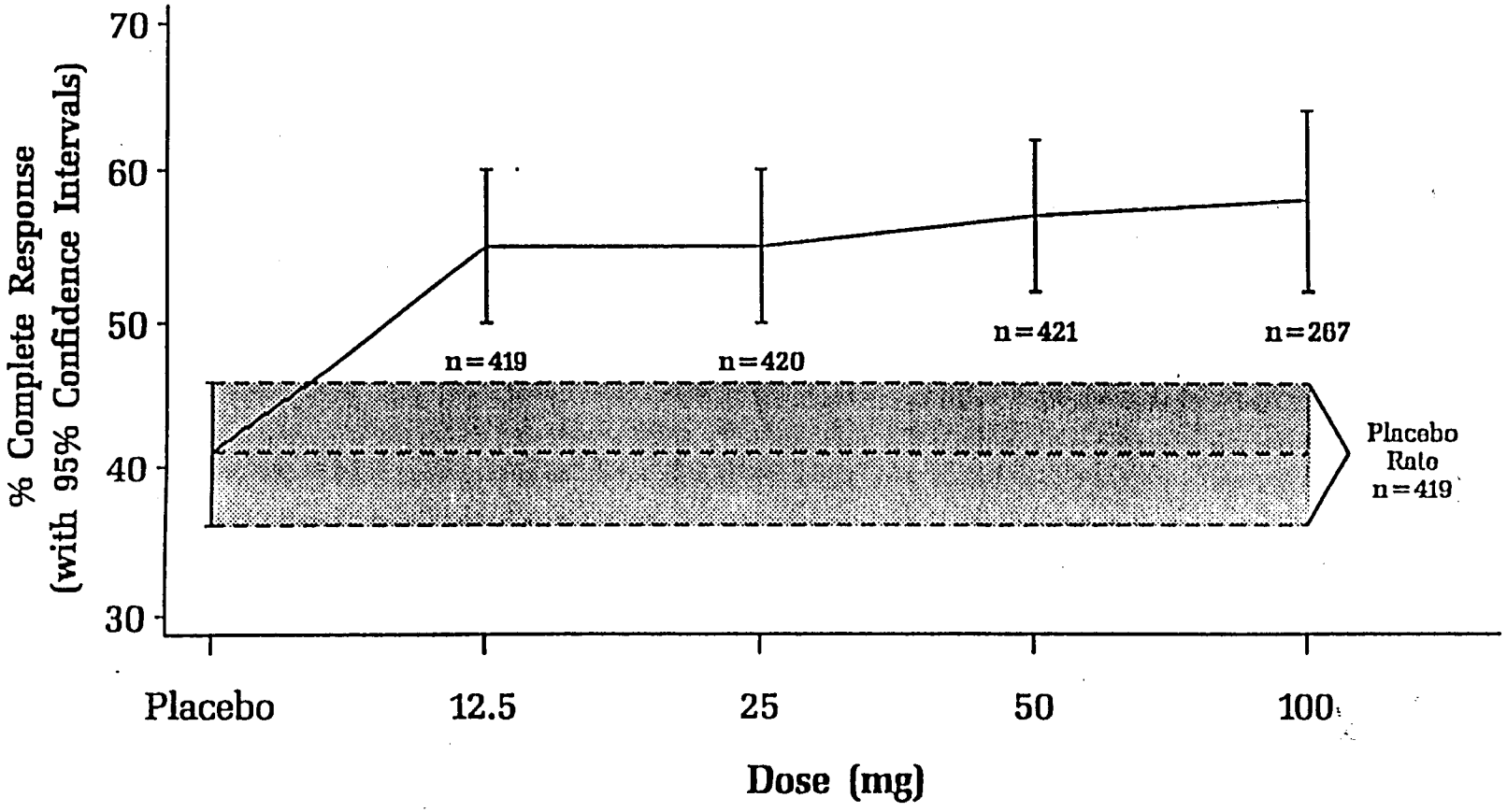
## % Complete Response by Study




SOURCE: MMD STAT_CDM NM08274 -IPONVT_EFF_2.SAS- (05JUN97, 16:01)

Figure 2a

# IV Dolasetron/PONV (Prevention)
# Randomized, Double Blind Trials
## Complete Response by Dose
### (12.5 vs Placebo, p=.0003)



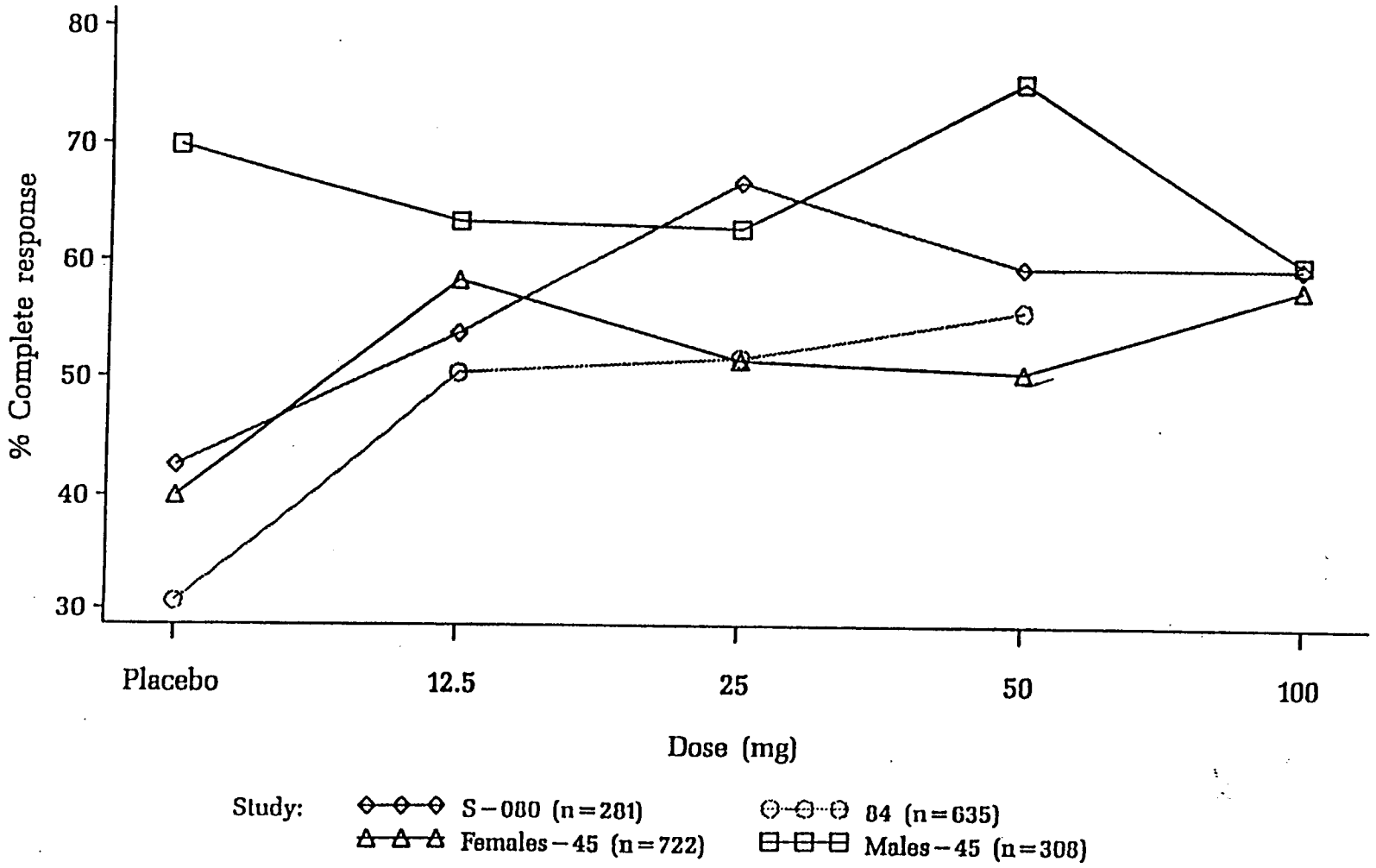

Includes studies MCPR0045, MCPR0084, 2-S-080

urce: MMD NM08274 - IVPONV_P.SAS - (04JUN97, 16:21)

Figure 2b

# IV PONV Prevention

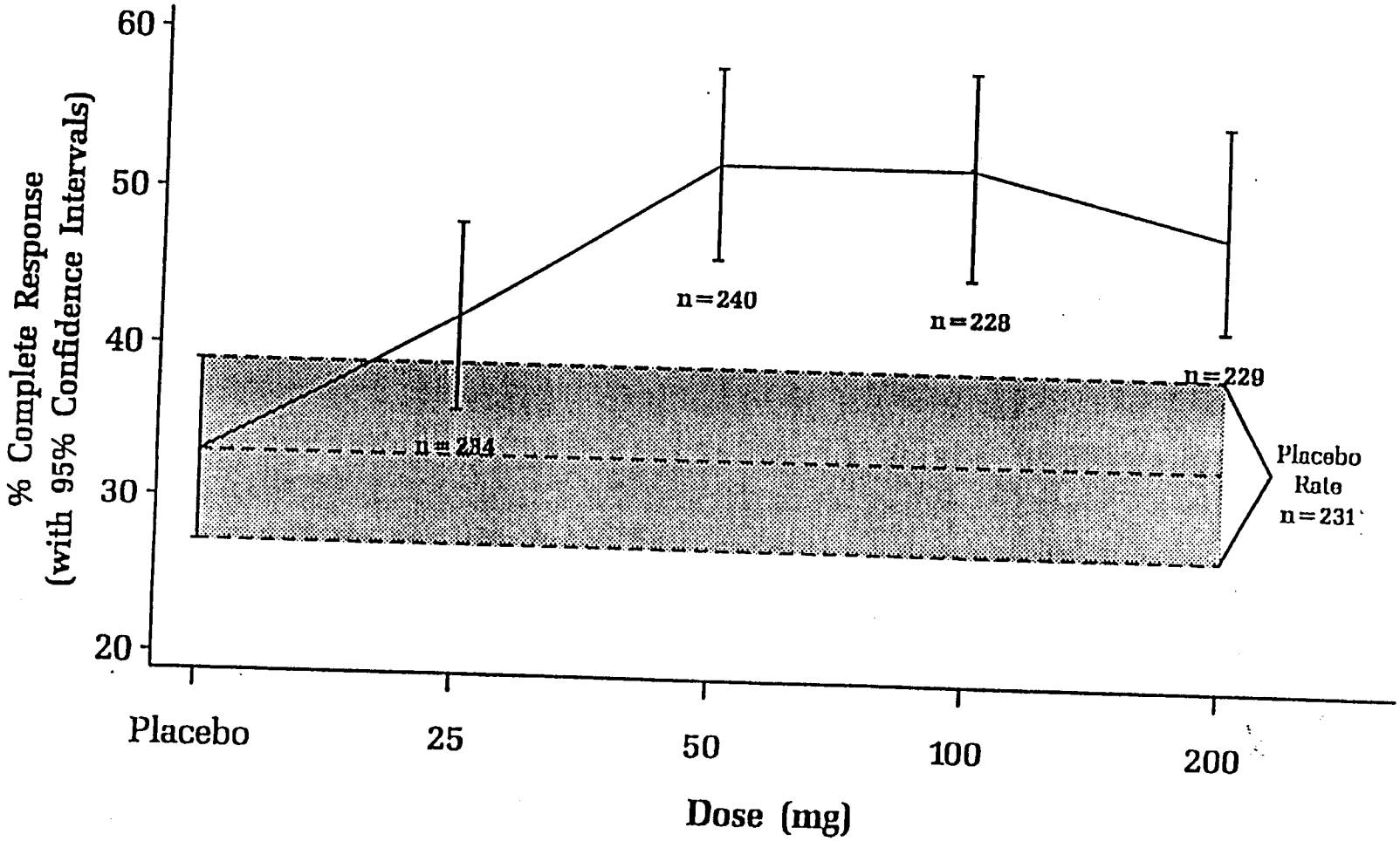
## % Complete Response by Study




SOURCE: MMD STAT_CDM NM08274 -IPONVP_EFF_1.SAS- (05JUN97, 16:03)

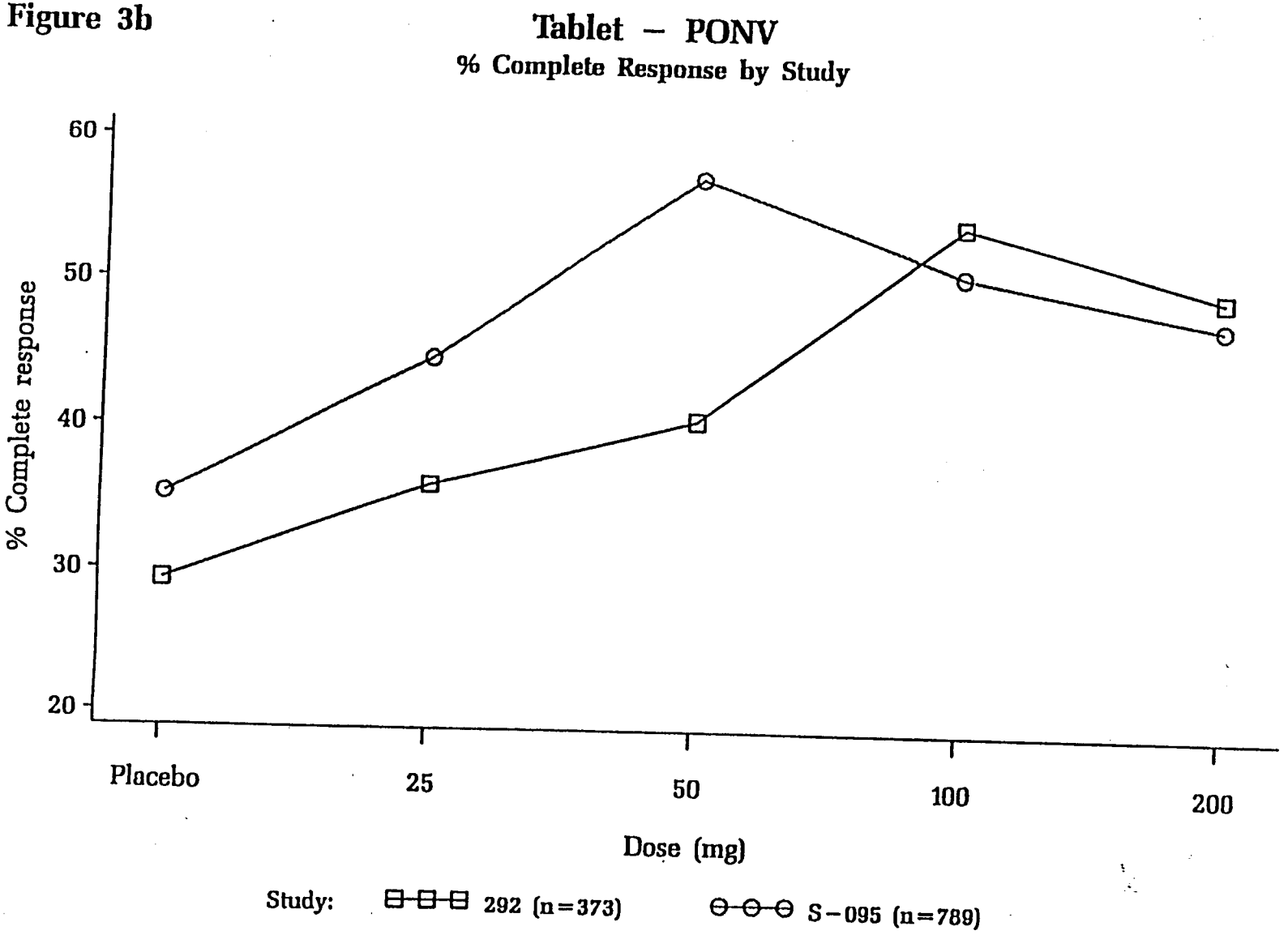
**Figure 3a**

## Oral Dolasetron/PONV (Prevention)
## Randomized, Double Blind Trials
### Complete Response by Dose




Source: MMD NM08274 – ORALPONV.SAS – (04JUN97, 16:21)

Figure 3b




SOURCE: MMD STAT_CDM NM08274 -OPONVP_EFF_3.SAS- (05JUN97, 16:04)