CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020623

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 20-623 **CHEMISTRY REVIEW #6** **REVIEW DATE:** 09/05/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC AMENDMENT	08/13/97	08/14/97	08/14/97

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
THERAPEUTIC CLASS: 1S

PHARMACOLOGICAL CATEGORY/INDICATION:
1. The prevention of nausea and vomiting associated with initial an repeated courses of emetogenic cancer chemotherapy.
2. The prevention of postoperative nausea and vomiting.

DOSAGE FORM: film-coated tablets
STRENGTHS: 50, 100, and 200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx
CHEMICAL NAME, STRUCTURE, MOL. FORMULA/WT: See Chem Review #1
SUPPORTING DOCUMENTS: See Chem Review #1
DOCUMENTS SUPPORTED: NDA 20-624, Dolasetron Mesylate Injection
RELATED DOCUMENTS: None
CONSULTS: See Chem Review #5

REMARKS/COMMENTS:
Based on the CMC information in the 06/25/97 amendment [Chem Review #5] the application was found acceptable with regard to Chemistry for APPROVAL (AP) for the 50 mg and 200 mg strengths.
This amendment is to add the 100 mg strength to the application.

CONCLUSIONS & RECOMMENDATIONS:
The CMC information in the proposed application is acceptable to support approval of the 50,100,200 mg tablets strengths with the initial expiry period for the 50,200 mg strength tablets as specified in Chem Reviews #3,#4,#5, and an

initial expiry period of **18M** for the 100 mg tablet strength in the proposed 5 count CR bottle, 10 count unit dose pack, and 5 count blister pack configurations.

/S/

09/05/97

Mike Adams
Review Chemist, HFD-180

/S/ 9/5/97

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

cc:
NDA 20-623
HFD-180/div file
HFD-180/MAdams
HFD-181/CSO
R/D Initial: EDuffy 9/5/97
Filename: MA/dob **F/T 9-5-97**\WP: c:\wpfiles\chem\N\20623709.6MA

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 20-623 **CHEMISTRY REVIEW #5** **REVIEW DATE:** 08/11/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC AMENDMENT	07/08/97	07/09/97	07/15/97

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
THERAPEUTIC CLASS: 1S

PHARMACOLOGICAL CATEGORY/INDICATION:
1. The prevention of nausea and vomiting associated with initial an repeated courses of emetogenic cancer chemotherapy.
2. The prevention of postoperative nausea and vomiting.

DOSAGE FORM: film-coated tablets
STRENGTHS: 50 mg and 200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Chem Review #1

SUPPORTING DOCUMENTS: See Chem Review #1

DOCUMENTS SUPPORTED BY THIS FILE:
NDA 20-624 Dolasetron Mesylate Injection

RELATED DOCUMENTS: None

CONSULTS:
Biopharm: See Chem Review #2
Statistics: See Chem Review #2
EER: All sites found acceptable 08/16/96
EA: Accepted in Chem Review #2

REMARKS/COMMENTS: None

CONCLUSIONS & RECOMMENDATIONS:

Based on the CMC information in the 06/25/97 amendment, the application is acceptable with regard to Chemistry for APPROVAL (AP).

/S/ 09/05/97

Mike Adams
Review Chemist, HFD-180

/S/ 9/5/97

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

cc:
NDA 20-623
HFD-180/div file
HFD-180/MAdams
HFD-181/CSO
R/D Initial: EDuffy 9/5/97
MA/dob **F/T 9-5-97**/WP: c:\wpfiles\chem\N\20623708.5MA

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

JUN - 6 1997

NDA 20-623 **CHEMISTRY REVIEW #4** **REVIEW DATE:** 5/20/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC AMENDMENT	04/24/97	04/25/97	05/01/97

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
THERAPEUTIC CLASS: 1S

PHARMACOLOGICAL CATEGORY/INDICATION:
1. The prevention of nausea and vomiting associated with initial an repeated courses of emetogenic cancer chemotherapy.
2. The prevention of postoperative nausea and vomiting.

DOSAGE FORM: film-coated tablets
STRENGTHS: 50 mg and 200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Chem Review #1

SUPPORTING DOCUMENTS: See Chem Review #1

DOCUMENTS SUPPORTED BY THIS FILE:
NDA 20-624 Dolasetron Mesylate Injection

RELATED DOCUMENTS: None

CONSULTS:

Biopharm:	See Chem Review #2
Statistics:	See Chem Review #2
EER:	All sites found acceptable 08/16/96
EA:	Accepted in Chem Review #2

REMARKS/COMMENTS:
This amendment is in response to the 04/04/97 letter.

CONCLUSIONS & RECOMMENDATIONS:
Based on the CMC information and data provided in the 04/24/97 amendment the application is APPROVABLE (AE) pending resolution of further CMC issues.

/S/ 6/6/97

Mike Adams
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/6/97

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

cc:
NDA 20-623
HFD-180/div file
HFD-180/MAdams
HFD-181/CSO
R/D Initial:EDuffy 6/5/97
MA/dob **F/T 6-6-97**\WP: c:\wpfiles\chem\N\20623705.4MA

APPEARS THIS WAY
ON ORIGINAL

APR - 4 1997

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 20-623 **CHEMISTRY REVIEW #3** **REVIEW DATE:** 02/27/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC AMENDMENT	01/23/97	01/24/97	02/03/97

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
THERAPEUTIC CLASS: 1S

PHARMACOLOGICAL CATEGORY/INDICATION:
1. The prevention of nausea and vomiting associated with initial an repeated courses of emetogenic cancer chemotherapy.
2. The prevention of postoperative nausea and vomiting.

DOSAGE FORM: film-coated tablets
STRENGTHS: 50 mg and 200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Chem Review #1

SUPPORTING DOCUMENTS: See Chem Review #1

DOCUMENTS SUPPORTED BY THIS FILE:
NDA 20-624 Dolasetron Mesylate Injection

RELATED DOCUMENTS: None

CONSULTS:
Biopharm: See Chem Review #2
Statistics: See Chem Review #2
EER: All sites found acceptable 08/16/96
EA: Accepted in Chem Review #2

REMARKS/COMMENTS:

This amendment is in response to the 12/24/96 letter.

CONCLUSIONS & RECOMMENDATIONS:

Based on the CMC information and data provided in the 01/23/97 amendment the application is APPROVABLE (AE) pending resolution of further CMC issues.

Mike Adams
Review Chemist, HFD-180

/S/ 4/4/97

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

cc:
NDA 20-623
HFD-180/div file
HFD-180/MAdams
HFD-181/CSO
R/D Initial: EDuffy 4-1-97
MA/dob **F/T 4-2-97**\WP: c:\wpfiles\chem\N\20623702.3MA

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 20-623 CHEMISTRY REVIEW #2 REVIEW DATE: 12/04/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AC AMENDMENT	09/12/96	09/13/96	unknown

NAME & ADDRESS OF APPLICANT:
Hoechst Marion Roussel, Inc.
Marion Park Drive
Kansas City, Missouri 64134

DEC 24 1996

DRUG PRODUCT NAME:
PROPRIETARY: ANZEMET
NONPROPRIETARY/USAN: Dolasetron Mesylate
CODE NAME: MDL 73,147EF.
THERAPEUTIC CLASS: 1S

PHARMACOLOGICAL CATEGORY/INDICATION:
1. The prevention of nausea and vomiting associated with initial an repeated courses of emetogenic cancer chemotherapy.
2. The prevention of postoperative nausea and vomiting.

DOSAGE FORM: film-coated tablets
STRENGTHS: 50,200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See NDA Chem Review #1

SUPPORTING DOCUMENTS: See NDA Chem Review #1

DOCUMENTS SUPPORTED BY THIS FILE:
NDA 20-624 Dolasetron Mesylate Injection

RELATED DOCUMENTS: None

CONSULTS:
Biopharm: Review completed 08/14/96 (R.Pradhan, HFD-870); comments included in 09/06/96 IR letter. See review comments below.
Statistics: Review of response in 09/06/96 IR letter completed 11/01/96. See review comments below.
EER: Response 08/16/96
EA: Information acceptable; FONZI prepared with this

review.

REMARKS/COMMENTS:

After the completion of NDA Chem Review #1, an in-house meeting was held to discuss the items in the Draft Deficiency Letter. Participating in the discussion were Dr. J.Gibbs (Deputy Director, ONDC III), Dr. E.Duffy (Chemistry Team Leader, HFD-180), K.Johnson (CSO, HFD-181), and myself. The items listed in review attachment 1 are those which had been included in the Draft Deficiency Letter were not included in the 09/06/96 IR letter to the firm.

This is in response to our 09/06/96 IR letter which requested a response ASAP.

CONCLUSIONS & RECOMMENDATIONS:

Based on the CMC information and data provided in the 09/12/96 amendment the application is APPROVABLE (AE) pending resolution of CMC issues.

/S/

12/24/96

Mike Adams

/S/

2/24/96

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

cc:
NDA 20-623
HFD-180/div file
HFD-180/MAdams
HFD-181/CSO
R/D Initial: EDuffy 12/ /96
Filename: N:\wpfiles\chem\N\20623612.2MA

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA 20-623 **CHEMISTRY REVIEW #1** **REVIEW DATE:** 07/09/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	09/29/95	10/02/95	10/16/96
BZ AMENDMENT[1]	01/16/96	01/17/96	01/29/96
BC AMENDMENT[2]	02/15/96	02/16/96	02/26/96
BC AMENDMENT[2]	03/01/96	unknown	unknown

1 Environmental Assessment information forwarded to consult reviewer - FONZI completed 6-17-96.

2 Stability information forwarded to consult reviewer - completed 8-11-96.

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
THERAPEUTIC CLASS: 1S

PHARMACOLOGICAL CATEGORY/INDICATION:
1. The prevention of nausea and vomiting associated with initial an repeated courses of emetogenic cancer chemotherapy.
2. The prevention of postoperative nausea and vomiting.

DOSAGE FORM: film-coated tablets
STRENGTHS: 25,50,100,200 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1H-indole-3-carboxylic acid, octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl ester, (2a,6a,8a,9ab)-, methanesulfonate, monohydrate

(2a,6a,8a,9ab)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate, methanesulfonate, monohydrate

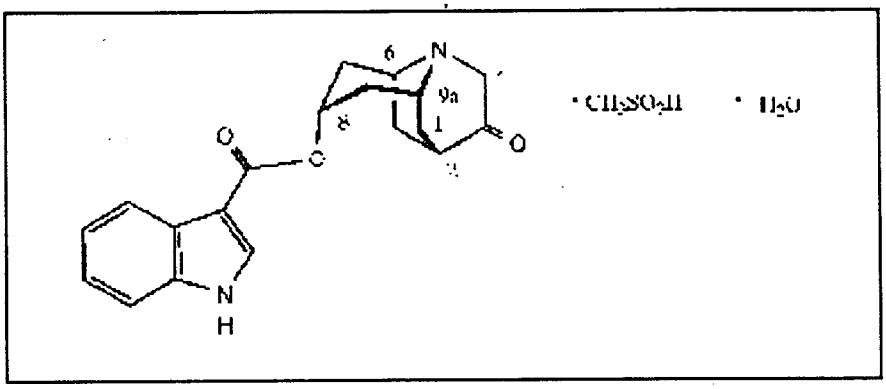
1H-indole-3-carboxylic acid, octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl ester, methanesulfonate, monohydrate

$C_{19}H_{20}N_2O_3$ CH_3SO_3H H_2O molecular weight = 438.50

CAS number = 115956-13-3

APPEARS THIS WAY
ON ORIGINAL

CAS stereochemistry and numbering system



SUPPORTING DOCUMENTS:

Number	Subject	Holder	Reference/LOA

DOCUMENTS SUPPORTED BY THIS FILE:
NDA 20-624 Dolasetron Mesylate Injection

RELATED DOCUMENTS: None

CONSULTS:

Biopharm: Review of 09/28/95 & 01/29/96 amendments completed 08/14/96 (R.Pradhan, HFD-870) with comments; see comments in drug product specifications section of review.

Statistics:
data has been reviewed and found to be inadequate to support NDA approval. Comments prepared for NDA action letter.

EER: EIR #9607 - acceptable/dated 8-19-96

EA: Acceptable, FONZI dated 6-20-96.

REMARKS/COMMENTS: NONE

CONCLUSIONS & RECOMMENDATIONS:

Based on the CMC information and data provided in the original submission dated 09/29/95 and in the amendments dated 01/16/96, 02/15/96 and 03/01/96, the application is NOT APPROVABLE (NA).

/S/ 09/05/96

Mike Adams

APPEARS THIS WAY ON ORIGINAL

/S/ 9/5/96

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

cc:
NDA 20-623
HFD-180/div file
HFD-180/MAdams
HFD-181/CSO/KJohnson
R/D Initial: EDuffy/8/30/96
MA/dob DRAFT 9-3-96**F/T 9-5-96**\WP: c:\wpfiles\chem\N\20623608.1MA

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

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

Nomenclature

Johnson

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.

APPEARS THIS WAY ON ORIGINAL

CDER Labeling and Nomenclature Committee

/S/ _____, Chair

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020623

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ANZEMET®

(Dolasetron mesylate)

Tablets 25, 50, 100, and 200 mg

NDA 20-623

Division of Gastro-Intestinal and Coagulation Drug Products

(HFD-180)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

C:\WPFILES\FONSI\20623.FPV

FINDING OF NO SIGNIFICANT IMPACT

ANZEMET®

(Dolasetron mesylate)

Tablets 25, 50, 100, and 200 mg

NDA 20-623

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(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Dolasetron mesylate is a chemically synthesized drug which is administered as 25, 50, 100, and 200 mg strength tablets 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 Marion Merrell Dow Inc., Cincinnati, Ohio. The finished drug product will be used throughout the United States in private homes and hospitals.

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. A major environmental depletion mechanism for dolasetron is aerobic biodegration in which the half-life of the drug substance was about 35 days. Therefore dolasetron is not expected to persist in the environment. Furthermore, dolasetron showed low toxicity to organisms in the environment, e.g. *Daphnia magna* (water flea) showed a 48-hour EC_{50} = 50 mg/L and No Observed Effect Concentration (NOEC) at 48-hours = 25 mg/L. In addition, bluegill fish showed a 96-hour LC_{50} of 21 mg/L and a 96-hour no observed effect level of 8.5 mg/L. The total amount of dolasetron that could be

emitted, assuming no metabolism or depletion, is several orders of magnitude value which defines a toxic substance. The data show that dolasetron is of relatively low toxicity to aquatic organisms and will not have significant environmental effects.

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. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

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.

/S/

6/20/96
DATE

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

APPEARS THIS WAY
ON ORIGINAL

6/20/96
DATE

/S/

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

APPEARS THIS WAY

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Exhibit 14: Dolasetron Mesylate Environmental Assessment FOI Copy

APPEARS THIS WAY
ON ORIGINAL

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Introduction and Summary

The aquisition of Marion Merrell Dow Inc. by Hoechst AG is currently in progress. Marion Merrell Dow Inc. is used interchangably with Hoechst Marion Roussel in this environmental assessment.

This environmental assessment (EA) is for dolasetron mesylate (Anzemet®) tablets. An NDA on dolasetron mesylate injection will be filed at a later date.

This environmental assessment follows the content and format described in 21 CFR § 25.30, specifically, Format 1 as described in 21 CFR §25.31 a. Based on the information provided herein the applicant concludes it has submitted sufficient information to provide a basis for the agency's determination to prepare a Finding of No Significant Impact (FONSI).

Dolasetron mesylate is indicated for use in the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy including high–dose cisplastin, the prevention of postoperative nausea and vomiting, and the treatment of postoperative nausea and vomiting.

Dolasetron mesylate drug substance will be manufactured at The Dow Chemical Company, Midland, Michigan. Dolasetron mesylate tablets will be manufactured and packaged by Marion Merrell Dow Inc., Cincinnati, Ohio. Rejected, expired, or returned goods will be returned to Marion Merrell Dow Inc., Kansas City, Missouri for evaluation, and materials identified for disposal will be shipped to ENSCO, Inc., El Dorado, Arkansas for incineration. Backup location for incineration is The Dow Chemical Company, Midland, Michigan. The manufacture of drug substance or drug product at each site will be conducted with sufficient controls to maintain compliance with applicable emissions requirements and will not impact compliance with the current emissions requirements at each site. There will be no significant impact on use of resources and energy at each site. The proposed action is not expected to have adverse effects on endangered or threatened species or historical sites near the Midland or Cincinnati manufacturing sites.

Dolasetron undergoes rapid and complete reduction of its ketone group to form the major active metabolite, MDL 74,156. Renal excretion is the major route of elimination and MDL 74,156 is excreted in the urine unchanged and also metabolized. MDL 74,156 contains the same chemical structure backbone as dolasetron and is expected to be more polar. Major metabolites of MDL 74,156 are also more polar than the parent compound. Therefore, results of dolasetron mesylate environmental fate and effects testing are extrapolated to the metabolites. In addition, a structure activity relationship indicates MDL 74,156 is not expected to be toxic to organisms in the environment.

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Dolasetron mesylate is freely soluble in water; is not expected to hydrolyze; has a partition coefficient log value of 2.28 at pH 7; has a low vapor pressure; and is not expected to photodegrade under normal environmental conditions. Based on these physical/chemical properties, environmental fate and effects studies were conducted in Tier 1, Aquatic Compartment and Tier 2, Terrestrial Compartment of the Environmental Assessment Testing Matrix.

Environmental fate testing included an aerobic biodegradation in water study, an aqueous photodegradation study, and a soil/sediment adsorption–desorption study. In the biodegradation in water study, the half–life of dolasetron mesylate was shown to be 35 days, suggesting significant removal in the waste water treatment plant (WWTP). In addition, the aqueous photodegradation study suggests a potential for extensive removal of dolasetron mesylate from the WWTP. The soil/sediment adsorption–desorption study indicated dolasetron mesylate is slightly mobile to immobile in soils.

Environmental effects testing included a microbial growth inhibition study, an acute toxicity study in *Daphnia magna*, an acute toxicity study in the bluegill fish (*Lepomis macrochirus*) and an acute toxicity study in the earthworm (*Lumbricus terrestris*.)

The Maximum Expected Emitted Concentration (MEEC) of dolasetron mesylate is calculated assuming no metabolism or depletion due to aquatic or terrestrial biodegradation processes. The MEEC [CONFIDENTIAL] is [CONFIDENTIAL]% of the no–observed effect concentration (NOEC) and [CONFIDENTIAL]% of the lowest EC_{50}/LD_{50} for the aquatic and terrestrial species tested. These percentages are [CONFIDENTIAL] orders of magnitude the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6). Therefore, the use of dolasetron mesylate is not expected to have significant adverse effects in the environment.

The alternative to the proposed action is non–approval and the prevention of dolasetron mesylate from being available for the use in the prevention and/or treatment of nausea and vomiting associated with cancer chemotherapy and operative procedures. Since the proposed action is not expected to have any significant adverse effects on the environment, no alternatives have been proposed.

E. Environmental Assessment

1. Date

September 29, 1995

2. Name of Applicant

Hoechst Marion Roussel

3. Address

9300 Ward Parkway
Kansas City, Missouri
64114–3321

4. Description of the Proposed Action

a. Description of Requested Approval/Need for the Proposed Action

The Applicant requests approval of a New Drug Application for dolasetron mesylate tablets for use in the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high–dose cisplastin, the prevention of postoperative nausea and vomiting, and the treatment of postoperative nausea and vomiting.

Dolasetron mesylate will be supplied as 25 mg, 50 mg, 100 mg, and 200 mg tablets. The recommended dosage is 100 mg.

The estimated annual production for the U.S. the first five years following approval of drug product is as follows:

Year	Tablet Sales			
	25 mg	50 mg	100 mg	200 mg
1997				
1998				
1999	[CONFIDENTIAL]	[CONFIDENTIAL]	[CONFIDENTIAL]	[CONFIDENTIAL]
2000				
2001				

b. Location Where Product Will Be Produced

i. Drug Substance

Dolasetron mesylate will be produced at The Dow Chemical Company, Midland, Michigan, 48674. The Michigan Division of The Dow Chemical Company is situated on approximately 1900 acres in the Saginaw Valley of mid–Michigan. The Tittabawasee River runs through the Michigan Division site. The manufacturing site is adjacent to Midland, Michigan which has a population of approximately 35,000. Wastes from the manufacture of dolasetron mesylate drug substance will be treated at the Michigan Division site of The Dow Chemical Company in Midland, Michigan.

ii. Drug Product

Dolasetron mesylate tablets will be manufactured and packaged by Marion Merrell Dow Inc., 2110 Galbraith Road, P.O. Box 156300, Cincinnati, Ohio, 45215. The plant site is located in Reading, Ohio, a suburb with a population of 12,000, located approximately 10 miles north of downtown Cincinnati. The site occupies approximately 58 acres and is zoned industrial. The immediate surrounding land is a mixture of light and heavy industry, business and residential use. A railroad runs through the site and a 4–lane highway borders the site on the east and south perimeters. The terrain surrounding the plant is gently rolling hills and the climate is temperate.

c. Locations of Product Use and Disposal of Rejected/Returned Goods

Dolasetron mesylate will be used by patients with nausea and vomiting in hospitals and/or in private homes throughout the United States.

Drug Substance

Rejected, returned or expired drug substance (if not reprocessed) at the Midland, Michigan manufacturing site will be incinerated at the at The Dow Chemical Incineration Complex:

The Dow Chemical Company, Midland, Michigan 48667
EPA ID No.: MID 000724724
Permitted by: State of Michigan Department of Natural Resources
Air Use Permit Nos.: 93–73, 471–79, 403–78, 403–78A, 678–83, 887–89, 441–88, 336–81A (no expiration)
Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)
Incinerator emission limits are given in ***Exhibit I, [CONFIDENTIAL].***

Rejected, returned or expired drug substance (if not reprocessed) at the Kansas City, Missouri manufacturing site will be incinerated at:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by: Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10–H, CSN 70–0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)
NPDES Permit: AR0037800 (expiration October 31, 1995)
Incinerator emission limits are given in ***Exhibit 2, [CONFIDENTIAL].***

Drug Product

Rejected, expired or returned drug product (if not reprocessed) will be returned to Marion Merrell Dow Inc., 10236 Marion Park Drive, Kansas City, Missouri 64137 for evaluation and disposal. Materials identified for disposal will be shipped to the following facilities for incineration:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by: Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10–H, CSN 70–0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)
NPDES Permit: AR0037800 (expiration October 31, 1995)
Incinerator emission limits are given in ***Exhibit 2, [CONFIDENTIAL].***

Back up location for incineration:

The Dow Chemical Company, Midland, Michigan 48667
EPA ID No.: MID 000724724
Permitted by: State of Michigan Department of Natural Resources
Air Use Permit Nos.: 93–73, 471–79, 403–78, 403–78A, 678–83, 887–89, 441–88, 336–81A (no expiration)
Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)
Incinerator emission limits are given in ***Exhibit 1, [CONFIDENTIAL].***

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

5. Identification of Chemical Substances That Are the Subject of the Proposed Action

a. Drug Substance

Chemical Names:

1*H*–Indole–3–carboxylic acid, octahydro–3–oxo–2,6–methano–2*H*–quinolizin–8–yl ester, (2α, 6α, 8α, 9aβ)–, monomethanesulfonate, monohydrate

(2α,6α,8α,9aβ)–Octahydro–3–oxo–2,6–methano–2*H*–quinolizin–8–yl–1*H*–indole–3–carboxylate monomethanesulfonate monohydrate

1*H*–Indole–3–carboxylic acid, octahydro–3–oxo–2,6–methano–2*H*–quinolizin–8–yl ester, methanesulfonate, monohydrate

Generic Name: Dolasetron mesylate

CAS Registry No: 115956–13–3

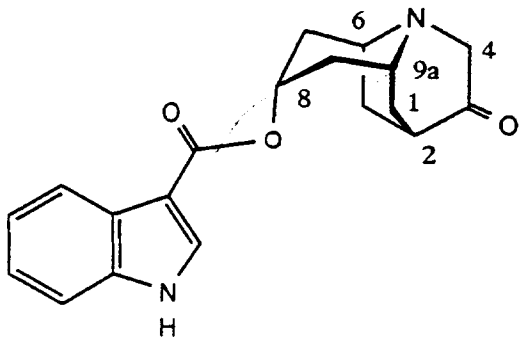
Code Number: MDL 73,147EF, MDL 73,147A (hydrochloride salt), MDL 73,147 (free base)

Molecular Weight: 438.50

Molecular Formula: $C_{19}H_{20}N_2O_3 \cdot CH_3SO_3H \cdot H_2O$

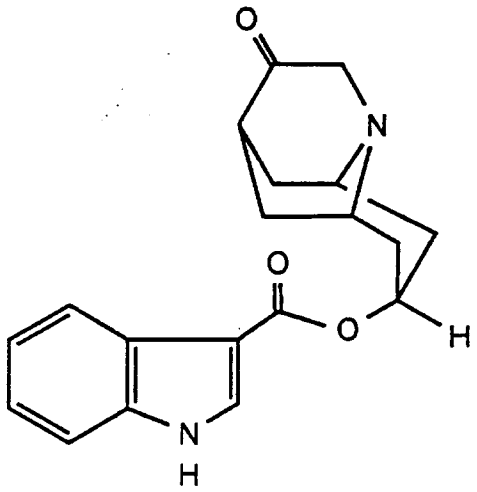
Chemical Structure:

The structure is portrayed below with stereochemistry and carbon number indications per CAS nomenclature.



$\cdot CH_3SO_3H \cdot H_2O$

The structure as portrayed below is another common representation of dolasetron mesylate.



$\cdot CH_3SO_3H \quad \cdot H_2O$

Physical Description: Dolasetron mesylate appears as a white to off–white powder. It is crystalline and is produced as the monohydrate.

A list of materials used in the preparation of the drug substance is included in ***Exhibit 3,*** *[CONFIDENTIAL].*

A list of drug substance impurities and degradation products is given in ***Exhibit 4,*** *[CONFIDENTIAL].*

b. Drug Product

Product Name: Anzemet®

A list of dosage form components is given in ***Exhibit 5, [CONFIDENTIAL], See FOI Attachment 1 (S3–V1.18–P302).***

6. Introduction of Substances into the Environment

a. Introduction From Manufacture of Drug Substance

Dolasetron mesylate will be produced at The Dow Chemical Company, Midland, Michigan, 48674. ***Exhibit 6, [CONFIDENTIAL],*** describes the chemical synthesis of dolasetron mesylate and the chemical substances which may be expected to be emitted to the atmospheric, aquatic and terrestrial compartments of the environment as a result of the bulk drug substance manufacturing process. The following provides details of the emissions in the air, aquatic, and terrestrial compartments as a result of the manufacture of the drug substance; statement of controls exercised; citation of and statement of compliance with applicable emissions requirements; and effect of approval on compliance with current emissions requirements.

i. Air Emissions

List of components of emitted streams:

Component	CAS No.	Max. Yearly Rate (lb/year)*
[CONFIDENTIAL]		

Statement of controls exercised:

Process vent gasses are treated with a C & H gas–fired thermal oxidizer with minimum design efficiency of 99.99%. Acidic process vent gasses are pretreated with a Jet–Vac Type W–40 hydrojet ejector venturi type scrubber using , NaOH scrubbing fluid with a design efficiency of 90%.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Air emissions are in compliance with the requirements set forth in The Dow Chemical Company Air Use Permit as granted by the State of Michigan Department of Natural Resources, Air Use Permit Nos. 803–84H and 552–93. The thermal oxidizer is operated according to the requirements set forth by the State of Michigan Department of Natural Resources Air Use Permit No. 64–76. Ash from the combustion process is disposed of in The Dow Chemical Company Salzburg Landfill, Midland, Michigan 48667. The Salzburg Landfill is operated according to the regulations set forth by the State of Michigan Department of Natural Resources, Hazardous Waste Facility Operating License EPA ID No. MID 890 617 435.

A signed statement of compliance for drug substance manufacture at the Midland site is included in ***Exhibit 7, [CONFIDENTIAL], see FOI Attachment 2 (S3–V1.18–P305).***

Effect of approval on compliance with current emission requirements at production site:

Production of ***[CONFIDENTIAL]*** of dolasetron mesylate will have no impact on compliance with current emission requirements. The total vent treatment for dolasetron mesylate will be less than 0.1% of that for the site.

ii. Aquatic Emissions

List of components of emitted streams:

Reference Waste Streams No. 3, 5, 7, and 9 on Dolasetron Mesylate Drug Substance Process Flow Chart (***Exhibit 8, [CONFIDENTIAL]***).

Component	CAS No.	Max. Yearly Rate (lb/yr)*
[CONFIDENTIAL]		

3. Chemistry, Manufacturing and Controls
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Statement of controls exercised:

The aqueous streams are discharged to The Dow Chemical Waste Water Treatment Plant (WWTP). The acids and bases are subsequently neutralized and both materials are discharged as dissolved solids from the WWTP to the Tittabawassee River in Michigan.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Aqueous discharge from The Dow WWTP is in compliance with the requirements set forth in the National Pollutants Discharge Elimination System (NPDES) Permit No. MI 40000868 for the Dow Chemical Waste Water Treatment Plant. Total dissolved solids daily maximum limit is 750 mg/L and total maximum monthly average is 500 mg/L.

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Exhibit 7, [CONFIDENTIAL], see FOI Attachment 2, S3–V1.18–P307.*

Effect of approval on compliance with current emission requirements at production site:

Production of [CONFIDENTIAL] of dolasetron mesylate will have no impact on compliance with current emission requirements. The total dolasetron mesylate waste streams for treatment will be less than 0.001% of that for the site.

iii. Terrestrial Emissions

List of components of emitted streams:

Reference Waste Streams No. 1, 2, 4, 6, 8 , and 10–23 on Dolasetron Mesylate Drug Substance Process Flow Chart (*Exhibit 8, [CONFIDENTIAL]*).

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Component	CAS No.	Max. Yearly Rate(lb/yr)*
[CONFIDENTIAL]		

Statement of controls exercised:

The waste streams listed above are incinerated at the Dow Chemical Incineration Complex. The thermal oxidizer operates at a minimum efficiency of 99.99%. Ash from the combustion process is disposed of in The Dow Chemical Company Salzburg Landfill, Midland, Michigan 48667. The Salzburg Landfill is operated according to the regulations set forth by the State of Michigan Department of Natural Resources, Hazardous Waste Facility Operating License EPA ID No. MID 890 617 435.

Citation of and statement of compliance with applicable emission requirements at federal, state and local levels:

The Dow Chemical Thermal Oxidation Unit Permit is operated according to the requirements set forth by the State of Michigan Department of Natural Resources in the Dow Chemical Incineration Complex Air Use Permit Nos. 336–81A, 93–73I, 471–79, 441–88 and State of Michigan Department of Natural Resources Hazardous Waste Facility Operating License EPA ID No. MID 000 724 724. The Dow Chemical Company Salzburg Landfill is operated according to the regulations set forth by the State of Michigan Department of Natural Resources, Hazardous Waste Facility Operating License EPA ID No. MID 890 617 435.

A signed statement of compliance for drug substance manufacture at the Midland site is included in *Exhibit 7, [CONFIDENTIAL], see FOI Attachment 2 (S3–V1.18–P305).*

Effect of approval on compliance with current emission requirements at production site:

Production of [CONFIDENTIAL] of dolasetron mesylate will have no impact on compliance with current emission requirements. The total dolasetron mesylate waste streams for treatment will be less than 0.1% of that for the site.

b. Introduction From Manufacture of Drug Product

Dolasetron mesylate tablets will be manufactured and packaged by Marion Merrell Dow Inc., 2110 Galbraith Road, P.O. Box 156300, Cincinnati, Ohio, 45215. These manufacturing operations are conducted according to current Good Manufacturing Practices and in compliance with applicable federal, state, and local laws and regulations.

Dolasetron mesylate 25 mg, 50 mg, 100 mg and 200 mg tablets will be packaged for commerce in bottles and in unit–dose blister packaging. Each bottle will be secured ; will be used on small bottles. A polypropylene, non–child resistant closure will be used on the bottles of 100 and 500 tablets. The unit–dose blister packaging will be used for commercial and sampling requirements.

The following provides details of the emissions in the air, aquatic, and terrestrial compartments as a result of the manufacture of the drug product; statement of controls exercised; citation of and statement of compliance with applicable emissions requirements; and effect of approval on compliance with current emissions requirements.

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

i. Air Emissions

List of components of emitted streams:

Reference Waste Stream No.1 on Dolasetron Mesylate Drug Product Process Flow Chart (*Exhibit 9, [CONFIDENTIAL]*).

Component	CAS No.	Max Yearly Rate Cincinnati (lb/yr)*	Midland**
[CONFIDENTIAL]			

Theoretical calculations are performed on the manufacturing process to determine potential emissions. A mass balance is completed for the manufacturing process in which losses are projected. If the manufacturing process has control on it, the destruction efficiencies are applied against the losses for the final emission quantity to the environment. Mathematically, this is shown as (process loss) x (removal/destruction efficiency) x (no. batches per year) = emissions per year.

Statement of controls exercised:

Compliance with air emission requirements is achieved either by operating discipline limiting flow rates and concentrations of air streams to within regulatory limits or by engineering controls for those air streams exceeding regulatory limits.

Emissions from the dolasetron mesylate tablet manufacturing process consist of exhausted air and water vapor, particulates, and organic material.

Compliance for particulate emissions is achieved through filters designed for 99% removal efficiency. Air streams are conveyed through these fabric filters before being released to the environment. The particulates held on the fabric filters are collected and disposed of in a licensed sanitary landfill.

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Volatile organic emissions are generated in the Quality Control laboratory process. Quality control analytical work will include typical analytical methods currently used to test existing products at this site. No new laboratory solvents will be required for this product. Assay, physical testing and stability testing will use small quantities of acetonitrile that may volatilize and be exhausted to the atmosphere. These laboratory operations are performed with local ventilation exhaust. Compliance with the organic emissions permit limit is achieved through engineering design and Good Laboratory Practices.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Emissions from the Cincinnati site processes are restricted by permits, rules, or acceptance criteria issued to the site by respective entities that are either a) responsible for ensuring environmental quality is not impaired or b) offsite waste management locations.

Air emissions are in compliance with the Federal Clean Air Act (Air Quality Implementation Plans for Ohio), Ohio EPA Laws and Regulations, OEPA APS Premise No. 1431380503, Permit No. P008, P009, and P014.

Permit #	Substance	Expected Emissions, Per Batch	Expected Emissions, Tons Per Year	Permit Limit, Tons Per Year
P008	Particulate	[CONFIDENTIAL]	[CONFIDENTIAL]	1.66
	Isopropyl alcohol			(exempt)
P009	Organic compounds:			4.38
	Acetonitrile			
P014	Particulate			1.01

A signed statement of compliance for drug product manufacture at the Cincinnati site is included in *Exhibit 10, [CONFIDENTIAL], see FOI Attachment 3 (S3–V1.18–P307).*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will not have a significant effect on compliance with the Cincinnati facility's current regulatory requirements.

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

ii. Aquatic Emissions

List of components of emitted streams:

Reference Waste Stream No. 2 on Dolasetron Mesylate Drug Product Process Flow Chart (*Exhibit 9, [CONFIDENTIAL]*).

Component	CAS No.	Max Yearly Rate Cincinnati (lb/yr)*	Midland**
[CONFIDENTIAL]			

Theoretical calculations are performed on the manufacturing process to determine potential emissions. A mass balance is completed for the manufacturing process in which losses are projected. If the manufacturing process has control on it, the destruction efficiencies are applied against the losses for the final emission quantity to the environment. Mathematically, this is shown as (process loss) x (removal/destruction efficiency) x (no. batches per year) = emissions per year.

Statement of controls exercised:

The Cincinnati site discharges its wastewater to a local publicly owned treatment works (POTW). Site discharges are allowed by permit and must be conducted in accordance with the POTW's rules and regulations. These pollutants are treated at the Metropolitan Sewer District of Greater Cincinnati POTW, 1600 Gest Street, Cincinnati, Ohio, 45204. The effluent is discharged to the Ohio River under a NPDES permit. The permit number is OH 1PM00001*GD, issued by Ohio Environmental Protection Agency.

Wastewater from the dolasetron mesylate tablet manufacturing process containing residual amounts of raw materials from equipment clean–up, coating solutions and wet dust collectors are sent to this local POTW. Less than one liter quantities of 0.1 N HCl is used in quality control assays and is neutralized before discharging to the sewer.

Equipment clean–up wastewater is pH adjusted onsite before being discharged to the local POTW. The cleaners used actually contribute to the pH and not the drug product itself.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Emissions from the Cincinnati site processes are restricted by permits, rules, or acceptance criteria issued to the site by respective entities that are either a) responsible for ensuring environmental quality is not impaired or b) offsite waste management locations.

Aquatic emissions are in compliance with the Federal Water Pollution Control Act, Ohio EPA Laws and Regulations (Water Pollution Control), the Metropolitan Sewer District (MSD) of Greater Cincinnati, MSD Rules and Regulations (Industry No. 09902355013, MSD Industrial Discharge Permit No. MIL–046).

For aquatic emissions, the POTW is issued a permit by Ohio EPA with specific limits. In turn, the POTW issues permits to industrial users with limits that must be met before discharge to the POTW.

The effluent from the Cincinnati site is routinely monitored by the Cincinnati site and the local POTW for the following parameters:

Permit #	Substance/Parameters	Expected Emission Levels/Conditions	Permit Limit	Est. Concentration
MIL–046	Cyanide	[CONFIDENTIAL]	15.9 mg/L	[CONFIDENTIAL]
	pH			
	Organics		450 mg/L	
	Oil and Grease		50 mg/L	
	Metals			
	Phenol		50 mg/L	
	Temperature		150° F	
* Not applicable				

Other parameters such as biochemical oxygen demand (BOD) and total suspended solids (TSS) have surcharge limits set by the POTW. Excess concentrations are acceptable and the facility is assessed a surcharge fee for treatment of the excess concentrations by the POTW.

A signed statement of compliance for drug product manufacture at the Cincinnati site is included in *Exhibit 10, [CONFIDENTIAL], see FOI Attachment 3 (S3–V1.18–P307).*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will not have a significant effect on compliance with the Cincinnati facility's current regulatory requirements.

iii. Terrestrial Emissions

List of components of emitted streams:

Reference Waste Stream No. 3 on Dolasetron Mesylate Drug Product Process Flow Chart *(Exhibit 9, [CONFIDENTIAL]).*

Component	CAS No.	Max Yearly Rate Cincinnati (lb/yr)*	Max. Yearly Rate Midland (lb/yr)**
[CONFIDENTIAL]			

Theoretical calculations are performed on the manufacturing process to determine potential emissions. A mass balance is completed for the manufacturing process in which losses are projected. If the manufacturing process has control on it, the destruction efficiencies are applied against the losses for the final emission quantity to the environment. Mathematically, this is shown as (process loss) x (removal/destruction efficiency) x (no. batches per year) = emissions per year.

Statement of controls exercised:

Solid wastes from the dolasetron mesylate tablet manufacturing process consist of less than one gram quantity of excipients from the Quality Control area, sludge (as total powders) from wastewater sump clean–outs and associated wastes from the manufacturing and packaging processes.

These wastes are collected and shipped off–site for recycling, or to an offsite licensed incinerator or landfill for disposal. The incinerator is operated by Dow Chemical USA, Saginaw Road, Midland, Michigan, 48667. The permit number is MID 000 724 724 and is issued by Michigan Department of Natural Resources. The landfill is operated by Rumpke Waste Systems, 10795 Hughes Road, Cincinnati, Ohio, 45251. Permit numbers are 05–3567 (Air), #1 (Solid Waste) and 1IN00180#AD (Wastewater) and are issued by Ohio EPA.

Citation of and statement of compliance with applicable emissions requirements at federal, state and local levels:

Terrestrial emissions are in compliance with the Federal Resource Conservation and Recovery Act (Solid waste Program: U.S. EPA ID No. OHD0004254702) and Ohio EPA Laws and Regulations (Ohio Hazardous Waste Permit No. 05–31–0515).

Terrestrial emissions are either recycled, incinerated or landfilled at offsite locations. These facilities have set parameters, limits or rules on waste acceptance criteria. Waste streams must be approved by these locations before wastes can be sent to them. This screening insures that these offsite locations maintain compliance with their specific permits.

A signed statement of compliance for drug product manufacture at the Cincinnati site is included in *Exhibit 10, [CONFIDENTIAL], see FOI Attachment 3 (S3–V1.18–P307).*

Effect of approval on compliance with current emission requirements at production site:

Approval of the proposed action will not have a significant effect on compliance with the Cincinnati facility's current regulatory requirements.

c. Employee Protection

Drug Substance Manufacturing Site:

Personnel in chemical production facilities are provided with appropriate personal protective equipment including safety glasses and goggles, safety shoes, protective gloves and clothing. Facilities and equipment are designed to minimize employee exposure to hazardous dust, fumes and vapors through engineering, work practices and administrative controls. Industrial hygiene monitoring of exposure to hazardous agents is routinely conducted at all production facilities. For certain non–routine or emergency situations, approved respiratory protection is provided to employees, and they are trained and fitted for use of the applicable respiratory protection device.

Employees are trained in the proper operation of equipment to minimize potential safety, health or environmental risks. Extensive safety training is mandated in all production facilities. Material Safety Data Sheets are available on–site for all chemicals handled in the production facilities.

Employees participate in periodic medical evaluations to elucidate clinical signs of occupational exposure. Findings of potential medical concerns are addressed by the company physicians at no cost to the employee.

Drug Product Manufacturing Site:

All associates receive extensive training for both normal and emergency situations as required to perform their respective operations. Associates receive general safety and chemical handling training as well as specialized training of the specific chemical hazards of the chemicals with which they work. Marion Merrell Dow Inc. provides worker protection by providing engineering controls wherever possible for potential hazards associated with noise, hazardous materials or ergonomic hazards. Associates are provided all necessary personal protective apparel to insure compliance with company requirements and that required by Occupational Safety and Health Act (OSHA), Hazard Communication Standard and Laboratory Standard. Also, emergency training and provisions are provided to respond in the event of injury, fire or chemical release to the air, water, or land as required under the applicable federal, state, and local laws.

Marion Merrell Dow Inc. has programs and procedures in place to anticipate and prevent potential adverse environmental impacts associated with this proposed action. Marion Merrell Dow Inc. has established emergency plans to be implemented in the event of an injury, spill or fire that may happen at any site or while being transported around the world. In–plant operation, including distribution and waste management operations, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency operations. Any incident that would require additional specialized expertise, would be provided by local fire, rescue, medical and emergency authorities or emergency response contract specialists.

d. Introduction From Disposal of Drug Substance and Drug Product

Drug Substance

Rejected, returned or expired drug substance (if not reprocessed) at the Midland, Michigan manufacturing site will be incinerated at the Dow Chemical Incineration Complex:

The Dow Chemical Company, Midland, Michigan 48667
EPA ID No.: MID 000724724
Permitted by: State of Michigan Department of Natural Resources
Air Use Permit Nos.: 93–73, 471–79, 403–78, 403–78A, 678–83, 887–89, 441–88, 336–81A (no expiration)
Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)
Incinerator emission limits are given in *Exhibit 1, [CONFIDENTIAL].*

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Rejected, returned or expired drug substance (if not reprocessed) at the Kansas City, Missouri manufacturing site will be incinerated at:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by: Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10–H, CSN 70–0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)
NPDES Permit: AR0037800 (expiration October 31, 1995)
Incinerator emission limits are given in *Exhibit 2, [CONFIDENTIAL].*

Drug Product

Rejected, expired or returned drug product (if not reprocessed) will be returned to Marion Merrell Dow Inc., 10236 Marion Park Drive, Kansas City, Missouri 64137 for evaluation and disposal. Materials identified for disposal will be shipped to the following facilities for incineration:

ENSCO, Inc., American Oil Road, P.O. Box 1975, El Dorado, Arkansas 71730
EPA ID No.: ARD069748192
Permitted by: Arkansas Department of Pollution Control and Ecology
Hazardous Waste Management Permit: 10–H, CSN 70–0098 (expiration June 26, 1998)
Construction and Operations Permit: 1009A (until terminated or modified)
NPDES Permit: AR0037800 (expiration October 31, 1995)
Incinerator emission limits are given in *Exhibit 2, [CONFIDENTIAL].*

Back up location for incineration of drug product:

The Dow Chemical Company, Midland, Michigan 48667
EPA ID No.: MID 000724724
Permitted by: State of Michigan Department of Natural Resources
Air Use Permit Nos.: 93–73, 471–79, 403–78, 403–78A, 678–83, 887–89, 441–88, 336–81A (no expiration)
Hazardous Waste Facility Operating License #: Incinerator Complex, Act 64, Operating License (expiration 9/27/94; license remains in effect due to submission of a complete reapplication in accordance with the appropriate license conditions and administrative rules)
Incinerator emission limits are given in *Exhibit 1, [CONFIDENTIAL].*

Trial burns conducted at the incinerators established maximum emission rates under worst case conditions; 99.99% destruction and removal efficiency (DRE) was demonstrated for principal organic hazardous constituents. Destruction efficiencies are controlled by EPA regulations pertaining to Resource Conservation and Recovery Act (RCRA) guidance 40 CFR 264 Subpart O.

e. Introduction From Use of Drug Product

Dolasetron mesylate is administered orally as a tablet and may be used by individuals at home or in a hospital setting. The estimated number of patients in the U.S. to be treated with dolasetron mesylate tablets annually ([CONFIDENTIAL]) represents a small percentage ([CONFIDENTIAL]%) of the U.S. population. The estimated market volume of dolasetron mesylate in the U.S. is [CONFIDENTIAL] tablets per year (based on 2001 projected sales), equivalent to [CONFIDENTIAL] dolasetron mesylate. Excreted drug substance would be introduced into the environment primarily through municipal sewage treatment plants or septic tanks.

Metabolism

The mass balance and metabolism of dolasetron mesylate has been evaluated and is reported in detail in Section 6, Human Pharmacokinetics and Bioavailability. The mass balance and metabolism of dolasetron mesylate is summarized below and reported in *Exhibit 11 ([CONFIDENTIAL])*.

Greater than 97% of the [14C]–radioactivity excreted in urine following oral and intravenous administration of [14C]–labeled dolasetron mesylate was accounted for by known metabolites, suggesting that all potentially relevant metabolites of dolasetron have been identified. The metabolism profile of dolasetron was similar for both oral and intravenous routes of administration.

Dolasetron undergoes rapid and complete reduction of its ketone group by carbonyl reductase to form the active metabolite, MDL 74,156. The complete reduction of dolasetron to MDL 74,156 is supported by the observations that dolasetron is not detected in urine (major elimination route for the dose), and the metabolites identified in urine are either MDL 74,156 or the metabolites of MDL 74,156.

MDL 74,156 is excreted in the urine unchanged and also metabolized by hydroxylation (5′and 6′ position), glucuronide conjugation, and N–oxidation, indicating that MDL 74,156 is eliminated by multiple routes. The N–oxidation of MDL 74,156 appears to be insignificant compared to other elimination routes as only 1% of urinary [14C]–radioactivity was accounted for by the N–oxide of MDL 74,156. MDL 74,156 is a major urinary metabolite comprising 53% to 61% of the species excreted in urine.

The 5′hydroxy–MDL 74,156 and 6′hydroxy–MDL 74,156 are excreted unchanged and also further metabolized to glucuronide and/or sulfate conjugates. The 5′hydroxy and 6′hydroxy metabolites of MDL 74,156 accounted for 3% to 5% and 7% to 13% of urinary [14C]–radioactivity, respectively. Total conjugates represented 26% of the excreted [14–C]–radioactivity in urine with MDL 74,156–glucuronide being a major conjugate (17.2%).

In contrast to dolasetron, MDL 74,156 has stereoisomers. More than 86% of MDL 74,156 excreted in urine was found to be R(+)–enantiomer for both oral and intravenous administration of dolasetron mesylate, suggesting that R(+) –MDL 74,156 is predominantly formed in the body.

MDL 74,156 contains the same chemical backbone as dolasetron and is expected to be more polar, because it is the reduced (alcohol) form of dolasetron which contains a ketone function. Major metabolites of MDL 74,156 are also more polar than the parent compound. Therefore, results of dolasetron mesylate environmental fate and effects testing are extrapolated to the metabolites. In addition, a structure activity relationship indicates the maximum expected emitted concentration (MEEC) of MDL 74,156 represents the following: [CONFIDENTIAL]% of the LC_{50} in fish; [CONFIDENTIAL]% of the LC_{50} in daphnids; [CONFIDENTIAL]% of the EC_{50} in green algae, and [CONFIDENTIAL]% of the predicted LC_{50} in saltwater fish. (*Exhibit 12, [CONFIDENTIAL]*). These percentages are well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

7. Fate of Emitted Substances in the Environment

Maximum Expected Emitted Concentration:

The maximum expected emitted concentration (MEEC) for the aquatic compartment (inlet to a typical WWTP) may be calculated by the following formula:

ppm (in environment) = (A) (B) (C) (D) (E) (F)

where A = pounds/year production
B = year/365 days
C = day person/150 gallons
D = 1/246 million persons (population of U.S., 1991)
E = gallons/8.34 pounds
F = one million

ppm (in environment) = pounds/year production x 8.9×10^{-9}

The MEEC for dolasetron mesylate based on the projected annual production of dolasetron mesylate in 2001 may be calculated as follows, assuming no metabolism or biodegradation:

MEEC (ppm) = kg/yr x 2.205 lb/kg x 8.9×10^{-9}

Dolasetron mesylate MEEC = [CONFIDENTIAL] kg/yr x 2.205 lb/kg x 8.9×10^{-9}
= [CONFIDENTIAL] ppm = [CONFIDENTIAL] mg/L

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Physical/Chemical Properties:

The physical and chemical properties of dolasetron mesylate have been evaluated and are reported in detail in the Chemistry, Manufacturing and Controls Section *(Section 3, [CONFIDENTIAL])* of the NDA document. Those data which are environmentally relevant are reported here, and in a data summary chart in *Appendix 15 (a) [CONFIDENTIAL], see FOI Attachment 5 (S3–V1.18–P317)*. Except where noted, studies were conducted by Marion Merrell Dow Inc., Cincinnati, Ohio or Kansas City, Missouri.

Water Solubility

The solubility of dolasetron mesylate in water is 280 mg/mL at 25° C *(Appendix 15 (b) i, [CONFIDENTIAL])*.

Hydrolysis

Dolasetron mesylate is not expected to hydrolyze due to the absence of hydrolyzable groups such as esters, amides, etc. The hydrolysis rate constant is estimated to be <10E–5/second.

Dissociation Constant

The pKa of dolasetron mesylate was determined over the temperature ranges 5° C to 45° C using solubility data *(Appendix 15 (b) ii, [CONFIDENTIAL])*. The values obtained are given in the following table:

Temperature (C)	pKa
5	6.919
15	6.649
25	6.398
35	6.164
45	5.946

n–Octanol/Water Partition Coefficient

The octanol/water partition coefficients of dolasetron mesylate were obtained over the pH range 1 to 10 at 25° C. The intrinsic partition coefficients were determined to be 0.82 and 240 for the charged and uncharged species respectively (log values of –0.086 and 2.38). Using these intrinsic values, partition coefficients of 0.817, 191, and 239 were calculated for pH 1.0, 7.0, and 10.0, respectively *(Appendix 15 (b) iii, [CONFIDENTIAL]).*

pH	K_{ow}	log K_{ow} (log P)
1.0	0.8170	–0.08780
7.0	191.4	2.282
10.0	239.0	2.378

Vapor Pressure

A study was conducted by The Dow Chemical Company, Midland, Michigan to measure the vapor pressure of dolasetron mesylate by the Knudsen–effusion/weight loss method. The vapor pressure of a sample of dolasetron mesylate was found to be 9.31×10^{-16} mmHg at 25° C *(Appendix 15 (b) iv, [CONFIDENTIAL]).*

Melting Temperature

Upon heating, dolasetron mesylate melts with decomposition at a DSC onset temperature of ca. 156° C *(Appendix 15 (b) v, [CONFIDENTIAL]).*

Ultraviolet–Visible Absorption Spectrum

Dolasetron mesylate shows ultraviolet absorbance spectroscopic maxima at 229 nm and 284 nm *(Appendix 15 (b) vi, [CONFIDENTIAL]).*

Conclusion

Based on the above physical/chemical properties of dolasetron mesylate, studies were conducted in Tier 1, Aquatic Compartment and Tier 2, Terrestrial Compartment of the Environmental Assessment Technical Test Matrix.

Environmental Fate Studies

Aerobic Biodegradation

An aerobic biodegradation study in water on [14C]–dolasetron mesylate was conducted *(Appendix 15 (b) vii, [CONFIDENTIAL]).* [14C]–dolasetron mesylate (retention time of approximately 9 min) was not significantly mineralized with 0.3% CO_2 production by day 28. Approximately 37.8 % of [14C]–dolasetron mesylate was biotransformed to a non–polar (retention time of approximately 15 min) degradation product, and approximately 2.0% to a more polar (retention time of approximately 4 min) degradation component. The biotransformation half–life was estimated to be approximately 35 days, suggesting that biodegradation in water may be a potential removal pathway.

Aqueous Photodegradation

A preliminary study on aqueous photodegradation revealed half–lives for [14C]–dolasetron mesylate of approximately 1.2 days in pH 5.0 buffer, 2.4 days in pH 7.0 buffer, and 3.5 days in pH 9.0 buffer. These results suggest a potential for extensive removal of dolasetron mesylate from the waste water treatment plant (WWTP). Assuming a residence time of 1 day within the aqueous component of WWTP for dolasetron mesylate and half–life of 4 days (worst case half–life), and the estimated MEEC of [CONFIDENTIAL], the expected environmental concentration (EEC) after photodegradation (assuming first–order degradation kinetics) is likely to be [CONFIDENTIAL], a reduction of [CONFIDENTIAL]. This EEC is several orders of magnitude lower than the NOEC for aquatic and terrestrial species.

Soil/Sediment Adsorption– Desorption

A soil/sediment adsorption–desorption study on dolasetron mesylate was conducted by *(Appendix 15 (b) viii, [CONFIDENTIAL]).* In clay loam, a K_{oc} value of 3855 indicates dolasetron mesylate would be slightly mobile in this type of soil. In sandy loam and silt loam the K_{oc} values of 25536 and 8066 indicate dolasetron mesylate would be immobile in these types of soil.

Predicted Environmental Concentrations of Dolasetron Mesylate

Air

Dolasetron mesylate's low vapor pressure and high water solubility preclude the air compartment from being affected by volatilization of this substance at the public sewage treatment plant. Manufacturing controls would prevent significant releases to the air during the manufacturing process.

Freshwater, Estuarine, and Marine Ecosystems

Since the majority of dolasetron mesylate will be discharged to public sewage treatment plants as a result of patient usage, environmental transport and biotransformation processes will occur first in the aquatic compartment. Dolasetron mesylate is not expected to hydrolyze under normal en-

vironmental conditions. However, as shown from the biodegradation in water study, the half–life of 35 days suggests significant removal in the WWTP. In addition, the aqueous photodegradation study suggests a potential for extensive removal of dolasetron mesylate from the WWTP. Environmental effects studies were conducted in aquatic organisms to correlate the predicted environmental concentrations with no–observed effects concentration (NOEC) and to assess risk as reported in *Section 8 of the Environmental Assessment.*

Terrestrial Ecosystems

The K_{oc} values determined by the soil/sediment adsorption–desorption study referenced above indicate dolasetron mesylate is slightly mobile in clay loam and immobile in sandy loam and silt loam. Due to the expected partitioning of dolasetron mesylate into the terrestrial compartment as a result of the observed strong adsorption to soil, two environmental effect studies (Microbial Growth Inhibition and Earthworm Toxicity) were conducted in the terrestrial compartment and are reported in *Section 8 of the Environmental Assessment.*

8. Environmental Effects of Released Substances

Expected Emitted Concentration:

The Expected Emitted Concentration (EEC) of dolasetron mesylate is calculated as follows:

EEC = MEEC – depletion due to aquatic or terrestrial biodegradation processes.

Assuming no biodegradation of dolasetron mesylate, EEC = MEEC = [CONFIDENTIAL] mg/L

Nonclinical Toxicology Studies with Dolasetron Mesylate:

An acute oral toxicity study in mice and rats was conducted by the Merrell Dow Research Institute, Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio *(Appendix 15 (b) ix, [CONFIDENTIAL])*. The acute oral LD_{50} of dolasetron mesylate in mice was 545 mg/kg in mice and 446 mg/kg in rats. The toxicology of dolasetron mesylate has been evaluated and is reported in detail in *Section 5, Nonclinical Pharmacology, Toxicology and Metabolism Section of the NDA.*

Aquatic Toxicology Studies with Dolasetron Mesylate:

Microbial Growth Inhibition:

A microbial growth inhibition study was conducted by
ppendix 15 (b) x, [CONFIDENTIAL]). No inhibition was observed for *Pseudomonas fluorescens, Azotobacter chroococcum, Aspergillus clavatus* and *Penicillium canescens* at any concentration of dolasetron mesylate up to and including 1000 mg/L. The MICs

for *Bacillus megaterium, Anabaena flos–aquae*, and *Chaetomium globosum* were 800, 200, and 800 mg/L, respectively.

The MEEC of dolasetron mesylate represents [CONFIDENTIAL]% of the MIC for *Anabaena flos–aquae*, the lowest MIC determined for the above microorganisms. This percentage is well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

***Daphnia magna*:**

An acute toxicity study in *Daphnia magna* was conducted by *(Appendix 15 (b) xi, [CONFIDENTIAL])*. The 48–hour EC_{50} was 50 mg/L. The 48–hour no–observed effect concentration was 25 mg/L.

The MEEC of dolasetron mesylate represents [CONFIDENTIAL]% of the acutely toxic level and [CONFIDENTIAL]% of the NOEC in *Daphnia magna*. These percentages are well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

Freshwater Fish:

An acute toxicity study in the bluegill fish (*Lepomis macrochirus*) was conducted by *(Appendix 15 (b) xii, [CONFIDENTIAL])*. The 96–hour LC_{50} was 21 mg/L. The 96–hour no–observed effect concentration was 8.5 mg/L.

The MEEC of dolasetron mesylate represents [CONFIDENTIAL]% of the acutely toxic level and [CONFIDENTIAL]% of the NOEC level in *Lepomis macrochirus*. These percentages are well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

Earthworm:

An acute toxicity study in the earthworm (*Lumbricus terrestris*) was conducted by *(Appendix 15 (b) xiii, [CONFIDENTIAL])*. The LC_{50} value for dolasetron mesylate could not be calculated for the 28–day exposure due to insufficient mortality but was >982 mg/kg soil. The NOEC for dolasetron mesylate was determined to be 241 mg/kg soil.

The MEEC of dolasetron mesylate represents [CONFIDENTIAL]% of the acutely toxic level and [CONFIDENTIAL]% of the NOEC in *Lumbricus terrestris*. These percentages are well below the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6).

Conclusion

The MEEC of dolasetron mesylate is calculated assuming no metabolism or depletion due to aquatic or terrestrial biodegradation processes. The MEEC ([CONFIDENTIAL]) is [CONFI-

DENTIAL]% of the NOEC and [CONFIDENTIAL]% of the lowest EC_{50}/LD_{50} for the aquatic and terrestrial species tested. These percentages are [CONFIDENTIAL] orders of magnitude less than the FDA one percent value which defines a toxic substance in 21 CFR 25.15 (b) (6). Therefore, the use of dolasetron mesylate is not expected to have significant adverse effects in the environment.

9. Use of Resources and Energy

a. Drug Substance

Midland, Michigan site:

The proposed action will not have a significant impact on total usage of energy or utilities by the Michigan Division site of The Dow Chemical Co., Midland, Michigan. The total steam and electrical power consumption for this purpose will be less than .01% of the overall site usage. No new land use will be required for the proposed new action.

The Michigan Department of Natural Resources Wildlife Division was contacted to determine if endangered or threatened species inhabit the area of drug substance manufacture. A search of the Michigan Natural Features Inventory database (Natural Heritage Program, Wildlife division) was conducted. The database indicated there are records of the threatened sedge *Carex serosa* in the Chippewa and Tittabawasee Rivers. The records documenting this species' presence are very old, and the Department of Natural Resources' assessment is the plant should not be impacted by the manufacturing site.

The National Register of Historic Places includes at least 17 listings of historical sites in Midland County, Michigan. Consultation with the Midland County Historical Society indicated the nearest historical site is approximately one mile from the plant's property. The proposed action is not expected to have a significant impact on these historical sites, as the controls on the manufacturing process should prevent any adverse effects to these sites.

b. Drug Product

Cincinnati, Ohio site:

The proposed action will not have a significant impact on total usage of energy or utilities by the Cincinnati site. The manufacturing process for dolasetron mesylate tablets is expected to utilize less than 1 % of the existing total site utilities usage. No new land use will be required for the proposed new action.

The area of the manufacturing site does not contain rare or unique species or species in danger of extinction. Consultation with the Ohio Department of Natural Resources indicated the manufac-

turing site is not a suitable habitat for rare or unique species, due to the site's extensive development.

There are at least 15 historical sites listed in the National Register of Historic Places in proximity to the manufacturing site. The nearest historical site is located approximately three miles from the manufacturing site. The proposed action will not have a significant impact on these sites, as the controls on the manufacturing process should prevent any adverse effects to these sites.

10. Mitigation Measures

Marion Merrell Dow Inc. has programs and procedures in place to anticipate and prevent potential adverse environmental impacts associated with this proposed action. Marion Merrell Dow Inc. has established emergency plans which are implemented in the event of an injury, spill or fire that may happen at any site or during transport around the world. All plant operations, including distribution and waste management, are carried out by trained personnel under the supervision of qualified personnel with training in both normal and emergency procedures. Material Safety Data Sheets for drug substance and drug product are available (*Exhibit 13, [CONFIDENTIAL], see FOI Attachment 4 (S3–V1.18–P309)*). Any incident that would require additional specialized expertise would be provided by local fire, rescue, medical and emergency authorities or emergency response contract specialists. Additionally, the worldwide emergency response capabilities of The Dow Chemical Company are available under written agreement with Marion Merrell Dow Inc.

11. Alternatives to the Proposed Action

The alternative to the proposed action is non–approval and the prevention of dolasetron mesylate from being available for the use in the prevention and/or treatment of nausea and vomiting associated with cancer chemotherapy and operative procedures. Since the proposed action is not expected to have any significant adverse effects in the environment, no alternatives are proposed.

12. List of Preparers

Marion Merrell Dow Inc., Kansas City, Missouri

Vicki J. Selzer, D.V.M.
Sr. Associate Scientist, Toxicology
D.V.M. Kansas State University College of Veterinary Medicine, 1985
B.S. Life Science and Physical Science, Kansas State University, 1980
9 Years Experience

Marion Merrell Dow Inc., Cincinnati, Ohio:

Teresa A. Turnbow, CHMM
Environmental Affairs Specialist
Certified Hazardous Materials Manager, Institute of Hazardous Materials Management
14 Years Experience

Dow Chemical Company, Midland, Michigan:

Charles Aiman, Ph.D.
Senior Associate Manufacturing Consultant
Ph.D. Chemistry, Universtity of Kansas, 1962
32 Years Experience

Persons and Agencies Consulted

Donald D. Fontaine, Ph.D.
Research Leader, Environmental Toxicology
Health and Environmental Sciences
The Dow Chemical Company
Midland, Michigan

George T. Chen, Ph.D.
Division of Gastrointestinal and Coagulation Drug Products, HFD–180
Food and Drug Administration
Rockville, Maryland

State of Michigan Department of Natural Resources,
Wildlife Division

Midland County (Michigan) Historical Society

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Ohio Department of Natural Resources

U.S. Department of Commerce
Bureau of the Census
Population Division

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3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

13. Certification

The undersigned officials of Hoechst Marion Roussel, Inc. certify that the information presented is true, accurate and complete to the best of the knowledge of Hoechst Marion Roussel, Inc.

Preparation of Environmental Assessment:

Signature: Vicki J. Selzer Date: 5/30/96

Vicki J. Selzer, D.V.M.
Sr. Associate Scientist, Toxicology

Review and Approval of Environmental Assessment:

Signature: Steven D. Barkyoumb Date: 5/30/96

Steven D. Barkyoumb, D.V.M., Ph.D.
Sr. Director, Drug Safety

Signature: Dhiren N. Shah Date: May 30, 1996

Dhiren N. Shah, Ph.D.
Director, Global Regulatory CMC

* Note the original certification found in Section 3, Volume 1.18 Page 300 was signed prior to the date referenced in item #1 of the Environmental Assessment. The date in item #1 was projected to correlate with the NDA submission date. The complete Environmental Assessment was officially signed off on June 28 and June 30, 1995. As requested by FDA May 16, 1996, the applicant can provide a certification reflecting today's date; however, the original certification is accurate.

14. References

The following references were used in the preparation of this Environmental Assessment and are generally available. Specific citations from these references may be obtained upon request.

1. **21 CFR Ch. 1 (4–1–93 Edition)**
Part 25 Environmental Impact Considerations
Food and Drug Administration, HHS

2. **40 CFR Ch. V (7–1–93 Edition)**
Part 1500 – 1508 Purpose, Policy and Mandate
Council on Environmental Quality

3. **Environmental Assessment Technical Assistance Handbook**
Food and Drug Administration
March 1987

4. **Pharmaceutical Manufacturer's Association**
Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA
July 1991

5. **Anzemet Global Forecasts**
June 15, 1994
Global Commercial Development
Marion Merrell Dow Inc.

6. **Structure Activity Relationships Program; Clement International Corporation**
Prepared for: Environmental Effects Branch
Health and Environmental Review Division
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency

7. **National Register of Historic Places**
Volume 1, 1976
Volume 2, 1976
1966 – 1991

8. **Rare and Endangered Species of Missouri**
Missouri Department of Conservation
1992, Conservation Commission of the State of Missouri

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Attachment 1: Dosage Form Components of Dolasetron Mesylate Tablets

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Dosage Form Components of Dolasetron Mesylate Tablets, continued

Chemical Substance	CAS Registry Number	Molecular Weight	Empirical Formula	Physical Description

* Removed during processing
** Not specified
*** Not applicable

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Attachment 2: Statement of Compliance, The Dow Chemical Company, Midland, Michigan

The Dow Chemical Company
Midland, Michigan 48667

November 2, 1994

DOLASETRON MESYLATE DRUG SUBSTANCE- ENVIRONMENTAL ASSESSMENT

Dolasetron mesylate drug substance is manufactured at the Dow Chemical Company's Michigan division facilities, Midland, Michigan, in compliance with all applicable state and federal environmental regulations.

The unlawful release of contaminants to the environment is prevented by the use of appropriate emission control devices such as vent gas scrubbers, particulate filters and activated waste water treatment.

The process to manufacture dolasetron meslylate drug substance is covered by Air Use Permits issued by the State of Michigan (Air Quality Division of the Michigan Department of Natural Resources pursuant to the delegation of authority from the Michigan Air Pollution Control Commission - Public Act 348, 1965, as amended); Air Use Permit No. 803-84H and No. 552-93. The process is in compliance with these rules, which are consistent with and at least as stringent as applicable federal standards under the Clean Air Act.

This process is in compliance with the Resource Conservation and Recovery Act (RCRA) of 1976, Title II (Solid Waste Disposal) and the State of Michigan Public Act 641, the Solid Waste Management Act.

The process is in compliance with the Federal Water Pollution Control Act and the Michigan Water Resources Commission Act (under the National Pollution Discharge Elimination System Permit No. MI 40000868).

D.C.Price
Manager
Pharmaceutical Chemicals Technology Center
827 Building
The Dow Chemical Co.
Midland, MI 48667

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Attachment 3: Statement of Compliance, Marion Merrell Dow Inc., Cincinnati, Ohio

MARION MERRELL DOW INC.

2110 East Galbraith Road
MAIL: P.O. Box 156300
Cincinnati, Ohio 45215-6300
Telephone: 513/948-9111
Telefax: 513/948-7076
Telex: 214320

Dolasetron Mesylate
Environmental Assessment
Certification of Compliance

The applicable Federal, State, and Local environmental regulations are:

AIR
Federal Clean Air Act
(Air Quality Implementation Plans for Ohio)

Ohio EPA Laws and Regulations
(Air Pollution Controls: OEPA APS Premise No. 1431380503)

WATER
Federal Water Pollution Control Act

Ohio EPA Laws and Regulations
(Water Pollution Control)

Metropolitan Sewer District of Greater Cincinnati (MSD) Rules and Regulations
(Industry No. 09902355013, MSD Industrial Discharge Permit No. MIL-046)

SOLID
Federal Resource Conservation and Recovery Act
(Solid Waste Program: U.S. EPA ID No. OHD004254702)

Ohio EPA Laws and Regulations
(Solid and Hazardous Waste Control: Ohio Hazardous Waste Permit No. 05-31-0515)

EMPLOYEE PROTECTION and COMMUNITY RIGHT TO KNOW
Superfund Amendments and Reauthorization Act of 1986, Title III,
Emergency Planning and Community Right-To-Know

Occupational Safety and Health Act (OSHA) of 1971
Hazard Communication Act of 1985

CERTIFICATION: The undersigned, Vice President, Operations, Marion Merrell Dow Inc., Cincinnati, Ohio, certifies that emissions, by-products or wastes resulting from the operations and disposal of this drug product, if conducted in a manner consistent with established procedures and practices at the Cincinnati plant, will be reduced, treated and/or disposed of in a manner which will comply with all applicable requirements and regulations pertaining to the Cincinnati plant.

DATE: 6/27/95

C. J. Portwood

Charles A. Portwood
Vice President, Operations

3. Chemistry, Manufacturing and Controls
E. Environmental Assessment

Attachment 4: MSDS for Dolasetron Mesylate Drug Substance and Drug Product

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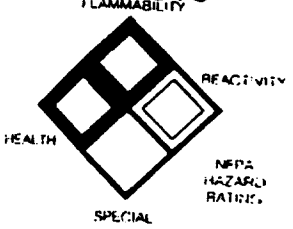
MATERIAL SAFETY DATA SHEET



PREPARATION DATE: 27 June, 1995

SECTION 1: Chemical Product and Company Identification

Common Name: (used on the label)	Dolasetron Mesylate
(Trade Name & Synonyms)	Dolasetron Mesilate, MDL73147EF
Chemical Name:	(2α, 6α, 8α, 9aβ)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate, monohydrate.
CAS Number:	115956-13-3
Molecular Formula:	$C_{19}H_{20}N_2O_3 \cdot CH_3SO_3H \cdot H_2O$
Molecular weight:	438.5
Manufacturer's Name:	Marion Merrell Dow
Address:	10236 Marion Park Drive Kansas City, Missouri 64137
Emergency Telephone Number:	816-966-5000
Other Information Calls:	816-966-5755

SECTION 2: Composition/Information on Ingredients

Material:	Dolasetron Mesylate
% Weight:	100
Nature of Hazard:	This material is a selective 5-HT_3-receptor antagonist-antiemetic.

SECTION 3: Hazards Identification

Appearance and Odor: White powder
Acute Exposure: Oral LD50 is 545 mg/kg for mice and 446 mg/kg for rats.

See Toxicological Information, Section 11.

SECTION 4: First Aid Measures

Inhalation: Breathe fresh air.
Eyes: Flush thoroughly with water for 15 minutes, seek medical attention.
Skin: Remove contaminated clothing, wash affected area with soap and water.
Ingestion: If large amount is ingested, seek medical attention.

SECTION 5: Fire Fighting Measures

Extinguisher Media: Carbon Dioxide, Dry Chemical Powder, Alcohol or Polymer Foam. Water may be effective for cooling.

Special Fire Fighting Procedures: Wear self-contained breathing apparatus and protective clothing to prevent contact with the skin.

SECTION 6: Accidental Release Information

Steps to be taken in case material is released or spilled: Sweep into suitable container and seal.
Waste Disposal Methods: Dispose according to local, state and/or federal regulations.

SECTION 7: Handling and Storage

Avoid contact with skin, or eyes.
Do not breathe the dust.
Hazardous polymerization: Will not occur.

SECTION 8: Exposure Controls/Personal Protection

If respiratory protection is required a NIOSH approved respirator, equipped with HEPA cartridges must be used.
Ventilation: Provide local exhaust ventilation to control airborne levels.
Protective gloves: Use gloves impervious to this material.
Safety glasses must be used when handling this material.
Additional protective clothing and equipment: Disposable jump suit.

OSHA Permissible Exposure Limit: Not available.
ACGIH Threshold Limit Value: Not available.
Chemical listed as a carcinogen or potential carcinogen: No.
National Toxicology Program: No.
I.A.R.C. Monographs: No.
OSHA: No.

SECTION 9: Physical and Chemical Properties

Appearance:	White powder
Odor:	None.
Physical State:	Solid.
Melting Point:	155°C-158°C

Solubility:

Water	>100 mg/mL
Methanol	>50 mg/mL
Propylene Glycol	>100 mg/mL
Hexane	$<5 \times 10^{-5}$ mg/mL

SECTION 10: Stability and Reactivity

Stability: Stable
Hazardous polymerization: Will not occur.

SECTION 11: Toxicological Information

Dogs dosed orally at >10 mg/kg/day had emesis and at >15 mg/kg/day displayed excessive salivation and/or tremors. Rats dosed IV at 60 mg/kg/day shower decreased activity, some convulsions, and an increased incidence of pulmonary granulomatous inflammation.

Animal reproduction studies have shown no evidence of teratogenicity when dolasetron mesylate was administered throughout organogenesis

No animal perinatal and postnatal toxicity was observed.

Dolasetron Mesylate was nonmutagenic in various in vitro and in vivo mutagenicity tests.

SECTION 12: Ecological Information

Not available.

SECTION 13: Disposal Considerations

Dispose of according to local, state, and/or federal regulations.

SECTION 14: Transport Information

This material is not regulated as hazardous by U.S.-DOT. A copy of this MSDS should accompany shipments of this material.

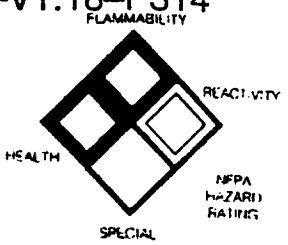
SECTION 15: Regulatory Information

No additional information at this time.

SECTION 16: Other Information

The information provided in this Material Safety Data Sheet has been compiled from our experience and the data presented in various technical publications. It is the users responsibility to determine the suitability of this information for the adoption of safety precautions as may be necessary. We reserve the right to revise the Material Safety Data Sheet from time to time as new information becomes available. The user has the responsibility to contact the company to make sure the sheet is the latest one issued.

MATERIAL SAFETY DATA SHEET



PREPARATION DATE: 27 June, 1995

SECTION 1: Chemical Product and Company Identification

Common Name: (used on the label)	Dolasetron Mesylate Tablets
(Trade Name & Synonyms)	Dolasetron Mesilate, MDL73147EF
Chemical Name:	(2α, 6α, 8α, 9aβ)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate, monohydrate.
CAS Number:	115956-13-3
Molecular Formula:	$C_{19}H_{20}N_2O_3 \cdot CH_3SO_3H \cdot H_2O$
Molecular weight:	438.5
Manufacturer's Name:	Marion Merrell Dow
Address:	10236 Marion Park Drive Kansas City, Missouri 64137
Emergency Telephone Number:	816-966-5000
Other Information Calls:	816-966-5755

SECTION 2: Composition/Information on Ingredients

Material:	Dolasetron Mesylate Tablets
% Weight:	Each tablet contains 25, 50, 100, or 200 mg dolasetron mesylate.
Nature of Hazard:	Pharmaceutical Product.

SECTION 3: Hazards Identification

Dolasetron Mesylate is a selective 5-HT_3-receptor antagonist-antiemetic.

SECTION 4: First Aid Measures

Inhalation: Breathe fresh air.
Eyes: Flush thoroughly with water for 15 minutes, seek medical attention.
Skin: Remove contaminated clothing, wash affected area with soap and water.
Ingestion: If large amount is ingested, seek medical attention.
In situations where overdose is suspected, supportive care is indicated. There is no known specific antidote.

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

Following a suspected overdose, it is recommended that an ECG be done, and if clinically indicated, the patient should have cardiac monitoring.

SECTION 5: Fire Fighting Measures

Extinguisher Media: Carbon Dioxide, Dry Chemical Powder, Alcohol or Polymer Foam. Water may be effective for cooling.

Special Fire Fighting Procedures: Wear self-contained breathing apparatus and protective clothing to prevent contact with the skin.

SECTION 6: Accidental Release Information

Steps to be taken in case material is released or spilled: Sweep into suitable container and seal.
Waste Disposal Methods: Dispose according to local, state and/or federal regulations.

SECTION 7: Handling and Storage

Store at room temperature.

SECTION 8: Exposure Controls/Personal Protection

OSHA Permissible Exposure Limit: Not available.

SECTION 9: Physical and Chemical Properties

Appearance: Tablets

SECTION 10: Stability and Reactivity

Stability: Stable
Hazardous polymerization: Will not occur.

SECTION 11: Toxicological Information

Animal reproduction studies have shown no evidence of teratogenicity when dolasetron mesylate was administered throughout organogenesis

No animal perinatal and postnatal toxicity was observed.

Dolasetron Mesylate was nonmutagenic in various in vitro and in vivo mutagenicity tests.

SECTION 12: Ecological Information

Not available.

SECTION 13: Disposal Considerations

Dispose of according to local, state, and/or federal regulations.

SECTION 14: Transport Information

This material is not regulated as hazardous by U.S.-DOT. A copy of this MSDS should accompany shipments of this material.

SECTION 15: Regulatory Information

No additional information at this time.

SECTION 16: Other Information

The information provided in this Material Safety Data Sheet has been compiled from our experience and the data presented in various technical publications. It is the users responsibility to determine the suitability of this information for the adoption of safety precautions as may be necessary. We reserve the right to revise the Material Safety Data Sheet from time to time as new information becomes available. The user has the responsibility to contact the company to make sure the sheet is the latest one issued.