CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020623

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-623 Submission Date: 9-28-95, 1-29-96
NDA 20-624 Submission Date: 2-19-96
ANZEMET®
Dolasetron Mesylate Tablet: 50 and 200 mg
Dolasetron Mesylate Injection: 12.5 mg (20mg/ml) single use ampule
100 mg/5 ml, 5 ml single use vial
200 mg/10 ml, 10 ml single use vial
Sponsor: Hoechst Marion Roussel, Inc.
Marion Park Drive, Kansas City, Missouri 64134

Priority: 1S
Reviewer: Rajendra S. Pradhan

Type of Submission: NME

Synopsis:

The sponsor has submitted the application NDA 20-623, dolasetron mesylate tablet (DM tablet), indicated for the *prevention* of nausea and vomiting associated with initial and repeat course of emetogenic cancer chemotherapy and the *prevention* of post operative nausea and vomiting (PONV). The sponsor has also submitted the application NDA 20-624, dolasetron mesylate injection (DM injection). The proposed indication is same as that of tablet in addition to being indicated for *treatment* of PONV. DM is a highly specific and selective serotonin subtype 3 (5-HT_3) receptor antagonist both in vitro and in vivo. Twenty-one definitive pharmacokinetic studies have been conducted by the sponsor to describe the human pharmacokinetics of dolasetron mesylate following oral and intravenous administration. Along with other supportive studies totalling 17, the sponsor has also conducted three population pharmacokinetic analysis and three pharmacokinetic-pharmacodynamic analysis.

Greater than 80% of ^{14}C-labelled DM, administered orally and IV, is excreted in urine and feces within 4 days. Renal excretion is a major elimination route for the administered ^{14}C-dose. All potentially relevant metabolites of dolasetron, both after oral and IV exposure, have been characterized. Dolasetron (parent drug) is rapidly (t1/2<10 minutes) and completely reduced to the major active metabolite, DMA, by carbonyl reductase, an ubiquitous enzyme. The active metabolite, DMA, is the most clinically relevant species. DMA is excreted unchanged or further metabolized by glucuronidation, hydroxylation, and to a minimal extent N-oxidation. The formation of DMA is stereoselective. The R(+)-enantiomer of DMA accounts for the majority of DMA present in plasma (>75%) and urine (>86%) following both oral and IV administration of DM. The "apparent" absolute oral bioavailability of DM, in healthy adult subjects, determined using plasma concentrations of the major active metabolite, DMA, is approximately 74%. The tablet formulation used in phase III efficacy and safety trial has been shown to be bioequivalent to to-be-marketed tablet. The plasma protein binding of DMA is approximately 69% in healthy volunteers and in cancer patients receiving

chemotherapy. The pharmacokinetics (PK) of dolasetron administered either intravenously or orally is linear over the dose range of 50 to 200 mg dolasetron mesylate.
The PK of DMA is similar between healthy adult volunteers and adult cancer patients receiving chemotherapy following both oral and IV administration of DM. In pediatric cancer patients, the apparent oral clearance of DMA increased approximately 2 fold (12-17 yr) to 3 fold (3 to 11 yr) and the apparent clearance of DMA increased approximately 1.3 fold (12 to 17 yr) to 2 fold (3 to 11 yr) compared to adult cancer patients or healthy subjects. The apparent oral clearance and apparent clearance of DMA for pediatric surgery patients (2 to 12 years) was approximately 1.3 and 1.4 times greater compared to adult healthy volunteers, respectively.
The PK of DMA is similar between male and female healthy volunteers and also similar between young (19 to 40 years) and elderly (≥65 years) healthy volunteers following both oral and IV administration of DM. The apparent oral clearance and apparent clearance of DMA decrease as renal function decreases and the apparent oral clearance of DMA decreases as hepatic function decreases. In CYPIID6 deficient subjects, following both oral and IV administration of DM, the systemic exposure of DMA increased by about two-fold with no difference in the incidences of adverse events compared to patients with no IID6 deficiency.

In a population PK analysis of 273 patients receiving cisplatin chemotherapy, value of DMA apparent systemic clearance (CLapp) and volume of distribution of central compartment (V) was estimated to be 0.607 L/hr/kg (%cv = 7.68) and 1.56 L/kg (%cv = 8.14), respectively. The intersubject variability in CLapp and V of DMA was 45.7 and 57.2%, respectively. The residual variability was 28.5%.

Increases seen in QTc intervals in healthy subjects and cancer patients were non-linearly related to increasing concentrations of DMA. There is a **linear relationship** between plasma concentrations of DMA and increases in QRS duration. The changes seen in JT interval were small and within the normal variation. The same was true for changes in heart rate. Therefore, it appears that increases in QTc interval after dolasetron mesylate administration are the result of increases in QRS duration (depolarization) and may not be because of any prolongation of JT interval (repolarization) or change in heart rate. Since higher concentrations of DMA are related to larger changes in QRS, DMA peak concentrations may be clinically more relevant than total systemic exposure.

DM is reduced completely to DMA in vivo by carbonyl reductase and DMA is eliminated by multiple routes. Therefore, the potential of other drug completely blocking elimination of DM is unlikely. In vitro data generated from liver microsomes suggest that the potential for DMA to inhibit in vivo metabolism of CYPIID6 and CYPIIIA substrates appears to be minimal since the inhibition constants 30 μM and 674 μM, respectively, are much greater than plasma concentrations of DMA observed after therapeutic doses of DM (2 μM upper limit). The mean steady-state plasma AUC (AUCss) and Cmax (Cmax,ss) of DMA increased 24% and 15%, respectively, when DM was coadministered with cimetidine, and decreased 28% and 17%, respectively, when DM was given with rifampin.

Recommendation:
The Human Pharmacokinetics and Biopharmaceutics portion of NDA 20-623 and NDA 20-624 is approved. Please forward the text under Comments (to be sent to Sponsor) and Labelling Comments (to be sent to Sponsor) to the Sponsor as appropriate.

APPEARS THIS WAY

/S/ 8-14-96

Rajendra S. Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

APPEARS THIS WAY
ON ORIGINAL

FT initialed by Lydia Kaus, Ph.D. /S/ 8/14/96

cc: NDA 20-623, 20-624, HFD-180, HFD-870 (MChen, Kaus, Pradhan), HFD-850 (Lesko), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), HFD-205 (FOI), Drug File (Clearance Bott)

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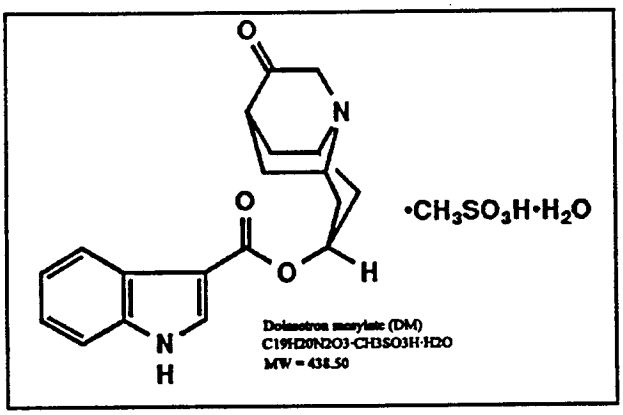
Background: Dolasetron mesylate (DM) is an antinauseant and antiemetic agent. It is a highly specific and selective serotonin subtype 3 ($5\text{-}HT_3$) receptor antagonist both in vitro and in vivo. The sponsor has submitted the application NDA 20-623, dolasetron mesylate tablet (DM tablet), indicated for the *prevention* of nausea and vomiting associated with initial and repeat course of emetogenic cancer chemotherapy and the *prevention* of post operative nausea and vomiting (PONV). The proposed dosage is 200 mg, given within 1 hr prior to chemotherapy and 50 mg within 2 hours prior to surgery (in pediatric patients 2 to 17 years of age the proposed dose is 2.4 mg/kg given one hour prior to chemotherapy and 1.2 mg/kg given 2 hours prior to surgery). The sponsor is seeking approval for 200 mg and 50 mg tablet strengths. The sponsor has also submitted the application NDA 20-624, dolasetron mesylate injection (DM injection). The proposed indication is same as that of tablet in addition being indicated for *treatment* of PONV. The proposed IV dose is 1.8 mg/kg given 30 minutes before chemotherapy for adults and children (2 - 17 yr). The proposed IV dose (infusion) is 12.5 mg given at the cessation of anesthesia (prevention) or as soon as nausea or vomiting presents (treatment). NDA's 20-623 and 20-634 are reviewed together as Section 6 of NDA 20-623 contained common pharmacokinetic and pharmacodynamic information for both the routes of administration.

Summary (Chemistry, Metabolism, Pharmacokinetics and Pharmacodynamics):

Dolasetron (DM) is a 5-HT3 receptor antagonist. Dolasetron mesylate (DMEF), the methanesulfonate salt of dolasetron, is under development worldwide by Marion Merrell Dow Inc. for the prevention of cancer chemotherapy-induced nausea and vomiting as well as the prevention and treatment of postoperative nausea and vomiting. DM has white to off-white appearance and has a solubility of greater than 100 mg/ml in water at 25 °C.



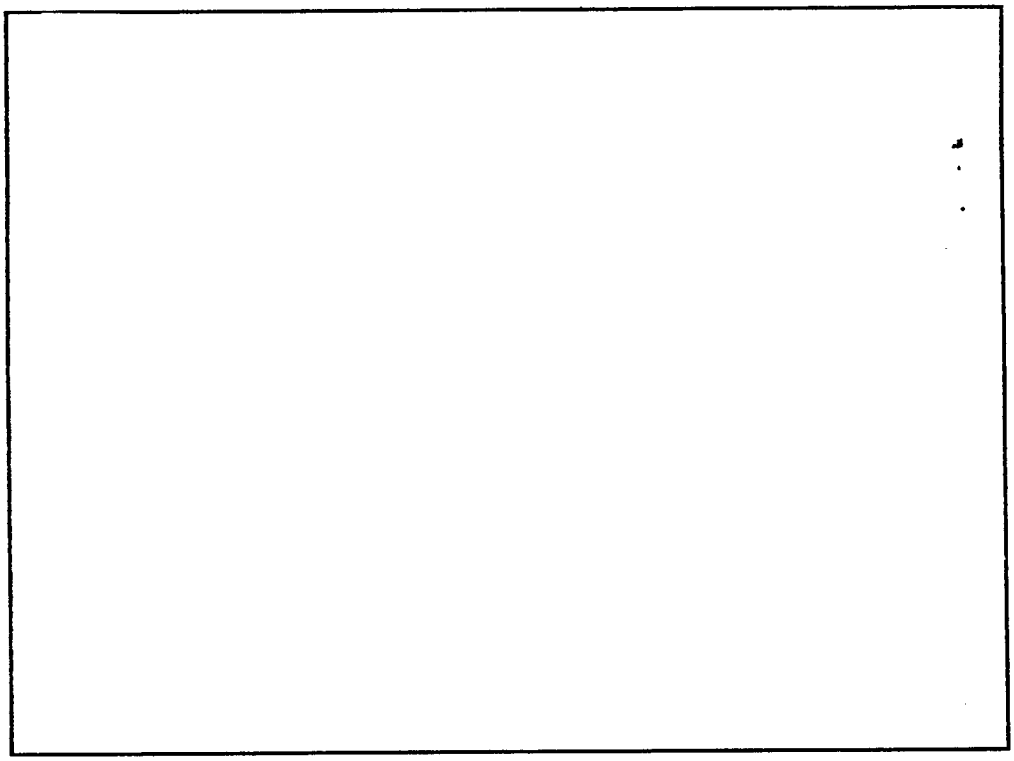
Twenty-one definitive pharmacokinetic studies have been conducted by Marion Merrell Dow Inc. to describe the human pharmacokinetics of dolasetron mesylate following oral and intravenous administration. Along with other supportive studies totalling seventeen, the data presented in this section support the following conclusions:

Mass Balance/Metabolism

- Greater than 80% of ^{14}C-labelled dolasetron mesylate, administered orally and intravenously, is excreted in urine and feces within 4 days.

Renal excretion is a major elimination route for the administered ^{14}C-dose.

- All potentially relevant metabolites of dolasetron, both after oral and intravenous exposure, have been characterized. Greater than 97% of the ^{14}C-radioactivity excreted in urine following oral and intravenous administration of ^{14}C-labelled dolasetron mesylate was accounted for by known metabolites. Dolasetron (parent drug) is rapidly ($t1/2 < 10$ minutes) and completely reduced to the major active metabolite, DMA. DMA is excreted unchanged or further metabolized by glucuronidation, hydroxylation, and to a minimal extent N-oxidation. The metabolism profile of dolasetron is identical for both oral and intravenous routes of administration.



- The reduction of dolasetron to DMA is mediated by a ubiquitous enzyme, carbonyl reductase. Cytochrome P450 (CYP) IID6 is primarily responsible for the hydroxylation of DMA and both CYPIIIA and flavin monooxygenase are responsible for the N-oxidation of DMA.
- DMA is excreted in the urine unchanged and also metabolized by hydroxylation (5'-OH and 6'-OH position), glucuronide conjugation, and N-oxidation, indicating that DMA is eliminated by multiple routes. The following table summarizes the percent contribution of DM and its metabolites to total ^{14}C-radioactivity excreted in urine over 24 hrs after dosing.

	IV Dose	Oral Dose
DM	ND	ND
DMA	53.0	60.9
5'-OH-DMA	5.1	3.4

6'-OH-DMA	13.2	6.7
DMA-N-oxide	-	1.0
Conjugates	26.1	26.1
DMA-Glucuronide		17.2
5'-OH-Glucuronide		5.6
6'-OH-Glucuronide		2.0
6'-OH-Glucuronide		1.3
Total ^{14}C-radioactivity Identified	97.4	98.1
ND: Not detected, *: Quantitation of N-oxide and each conjugate was not performed for the IV dose		

- Dolasetron is rarely detected in plasma after oral administration and accounts for only 2.2% of circulating species in plasma after intravenous administration. DMA is the major metabolite of dolasetron representing of all circulating species in plasma. Plasma AUC contribution of R(+)-DMA, the more potent enantiomer, is approximately 3- to 4-fold greater than the S(-)-enantiomer. The 5'-OH hydroxy-DMA and 6'-OH hydroxy-DMA represent less than 10% of all circulating species. Based on the composition of urinary metabolites, most of the unidentified plasma ^{14}C-radioactivity : speculated to be attributed to the conjugates of DMA and hydroxylated DMA.
- Based on the relative in vitro pharmacological activity and systemic exposure (i.e., plasma AUC) of parent drug and metabolites, DMA is the most clinically relevant species responsible for the majority of clinical antiemetic activity as well as cardiac conduction changes observed following oral and intravenous administration of dolasetron mesylate.

Absorption/Biopharmaceutics: The "apparent" absolute oral bioavailability of dolasetron mesylate, in healthy adult subjects, determined using plasma concentrations of the major active metabolite, DMA, is approximately 74%. The apparent relative bioavailability of dolasetron mesylate tablets to the solution administered orally is approximately 100%.

- Tablets used in phase III clinical safety and efficacy trials, tablets proposed for market, and the intravenous solution of dolasetron mesylate administered orally are bioequivalent.
- When proposed marketed DM tablet was given with a high fat meal (standard NDA high fat breakfast) DMA $AUC_{0-\infty}$ decreased by 12.5 % and DMA Cmax decreased by 26 %. However, considering the circumstance under which DM will be administered (Chemotherapy or surgery), mentioning this food effect in the labelling may not be relevant.

Distribution/Protein Binding: Dolasetron and DMA are widely distributed in the body with an apparent volume of distribution of and , respectively in healthy adult subjects. The distribution of dolasetron and its metabolites to blood cells is not extensive as a blood to plasma distribution ratio of ^{14}C-radioactivity is approximately one.

- The plasma protein binding of DMA is approximately 69% in healthy volunteers and in cancer patients receiving chemotherapy (determined by equilibrium dialysis). Since DMA is not highly

bound to plasma proteins including albumin and α1-acid glycoprotein, no clinically significant changes in plasma protein binding of DMA are expected in renally or hepatically impaired subjects and subjects undergoing surgery.

Pharmacokinetics/Dose Proportionality: Dolasetron is rarely detected in plasma following oral administration of 50 to 200 mg dolasetron mesylate and rapidly ($t1/2 < 10$ minutes) eliminated from plasma following intravenous administration. The pharmacokinetics of dolasetron is linear over the intravenous dose range of 50 to 200 mg dolasetron mesylate.

- DMA is formed rapidly ($tmax < 1$ hour) following both oral and intravenous administration of dolasetron mesylate and eliminated with a terminal elimination half-life of 7 to 9 hours. DMA exhibits linear pharmacokinetics over the oral and intravenous dose range of 50 to 200 mg dolasetron mesylate. Single dose pharmacokinetics of DMA are predictive of steady-state systemic exposure of DMA following once daily oral doses of dolasetron mesylate (it should be noted that DM will not be administered on a QD regimen).

Pharmacokinetics of Stereoisomers: The formation of DMA is stereoselective. The R(+)-enantiomer of DMA accounts for the majority of DMA present in plasma (>75%) and urine (>86%) following both oral and intravenous administration of dolasetron mesylate. The pharmacokinetics of R(+) and S(-)-DMA are linear over the dose range of 50 to 200 mg dolasetron mesylate.

- The urinary excretion ratios of R(+) and S(-) to total DMA following oral and intravenous administration of dolasetron mesylate were similar between healthy male volunteers and special populations such as females, elderly, renally impaired subjects, and cytochrome IID6 deficient subjects and is not affected by coadministration of a cytochrome P450 inhibitor (cimetidine) and inducer (rifampin).

Mean (%CV) Pharmacokinetic Parameters of R(+) and S(-)-DMA Following Intravenous and Oral Administration of Dolasetron Mesylate; Treatment A: 200 mg (2.54 mg/kg) IV, B: 100 mg (1.27 mg/kg) IV, C: 50 mg (0.64 mg/kg) IV, D: 200 mg PO, N=12

Parameter	TRT	Mean (% CV)	
		R(+) DMA	S(-) DMA
AUC_{0-} (ng.h/ml)	A	2801 (23)	765 (16)
	B	1310 (28)	392 (24)
	C	645 (20)	209 (24)
	D	2101 (29)	526 (21)
Cmax (ng/ml)	A	554 (29)	88 (21)
	B	273 (32)	46 (20)
	C	150 (34)	29 (37)
	D	523 (41)	105 (26)
Urinary Excretion (% of dose)	A	29.3 (30)	3.5 (23)
	B	25.6 (36)	3.3 (26)
	C	26.0 (29)	3.4 (29)
	D	18.7 (33)	2.9 (23)

Pharmacokinetics in Patients: The pharmacokinetics of DMA is similar between healthy adult volunteers and adult cancer patients receiving chemotherapy following both oral and intravenous administration of dolasetron mesylate.

Adult Cancer Patients:
The population pharmacokinetics of DMA after intravenous administration of dolasetron mesylate were investigated in 273 cancer patients receiving cisplatin chemotherapy (70 mg/m2) in a multicenter dose-response efficacy trial (study MCPR0032). The patients received a 0.6, 1.2, 1.8, 2.4, or 3.0 mg/kg dose of dolasetron mesylate by an intravenous infusion over 9 to 30 minutes, and 5 serial blood samples were obtained from each patient after dosing. Plasma DMA concentration-time data were analyzed by nonlinear mixed effect modeling (NONMEM).

The population pharmacokinetics of DMA for cancer patients after intravenous administration of DM was best described by a two-compartment model, and the estimated population pharmacokinetic parameters for DMA were as follows:

CL_{app} (L/h) = 0.607·WGT(kg)·(1+0.303·*RACE*-0.184·*ATEN*)-0.090·*CRET(μmol/L)*
V (L) = 1.56·*WGT(kg)*
Q (L/h) = 39
V_{ss} (L) = 4.1·*WGT(kg)*

where CLapp is the apparent clearance, Q is intercompartmental clearance, V and Vss are the apparent volume of distribution of the central compartment and at steady-state, respectively. The PK of DMA in cancer patients was linear over the intravenous dose range of 0.6 to 3.0 mg/kg DM. Patient age, gender, dose of cisplatin, and concomitant drugs such as furosemide, nifedipine, diltiazem, ACE inhibitors, verapamil, glibenclamide, and propranolol had no effect on CLapp of DMA, while patient body weight (WGT), race (RACE), serum creatinine concentration (CRET), and atenolol coadministration (ATEN) were observed to influence CLapp of DMA and patient body weight influenced V and Vss of DMA.
The apparent clearance values of DMA for cancer patients, estimated by posthoc analysis in NONMEM, are summarized in the following table. The mean CLapp value of DMA increased 17% in Blacks and decreased 27% in patients on atenolol medication.

	Cancer Patients				Healthy Normal Volunteers (N=24)
	Other Race (Not on Atenolol) (N=240)	Other Race (on Atenolol) (N=6)	Blacks (Not on Atenolol) (N=27)	Overall (N=271)	
Mean	10.1	7.4	11.8	10.2	9.4
Range					

However, the CLapp differences observed due to race and atenolol coadministration should be judged by the Medical Officer (HFD-180) as the ranges of CLapp values obtained for Blacks

X

and patients on atenolol medication) were similar to that obtained for the patients not belonging to either group). According to the Div. of Pharmaceutical Evaluation II (DPE-II) a 30 % dose reduction of DM when given concurrently with atenolol is necessary.

The sponsor studied the population PK of DMA after oral administration of DM in two additional clinical studies viz. MCPR0043, N=67, patients on carboplatin or cisplatin containing therapy, and MCPR0048, N=61, patients on cyclophosphamide and/or doxorubicin containing therapy. These studies were considered as secondary because of the sampling strategy used and small number of patients. Plasma samples were not obtained during the absorption phase of DM.

Pediatric Cancer Patients:

In pediatric cancer patients, the apparent oral clearance of DMA increased approximately 2 fold (12-17 yr) to 3 fold (3 to 11 yr) and the apparent clearance of DMA increased approximately 1.3 fold (12 to 17 yr) to 2 fold (3 to 11 yr) compared to adult cancer patients or healthy subjects.

Oral Dose: The PK of DMA after oral administration of DM was studied in 32 pediatric cancer patients (3 to 17 years old) receiving chemotherapy in a multicenter clinical trial (study AN-PD-0292). The patients received an oral dose of 0.6, 1.2 or 1.8 mg/kg DM. The PK parameters of DMA are summarized in the following table.. **It should be noted that the sponsor's proposed oral dose for pediatric cancer patients, 2.4 mg/kg, was not studied.**

Parameter	Pediatric Patients Dose (Oral)			Healthy Adult Volunteer Dose (Oral)		
	0.6 mg/kg N=9	1.2 mg/kg N=13	1.8 mg/kg N=10	0.65 mg/kg N=17	1.3 mg/kg N=16	2.6 mg/kg N=17
Cmax (ng/ml)	54.7 (38)	135.4 (52)	264.0 (58)	106.9 (20)	224.6 (24)	520.4 (26)
tmax (h)	1.0 (50)	0.9 (56)	0.9 (55)	0.72 (24)	0.70 (30)	0.81 (14)
AUC_{0-} (ng.h/ml)	252.8 (46)	578.0 (72)	1085.3 (79)	613.3 (42)	1181.4 (39)	2735.1 (38)
$t_{1/2}$ (h)	5.21 (30)	6.07 (39)	6.19 (34)	7.74 (36)	7.47 (21)	8.86 (19)
$CL_{app,po}$ (ml/min/kg)	37.4 (58)	40.4 (61)	32.4 (58)	15.2 (38)	15.5 (35)	13.3 (36)

IV Dose: The PK of DMA after intravenous administration of DM was studied in 46 pediatric cancer patients (3 to 17 years old) receiving chemotherapy in a multicenter clinical trial (study AN-PD-0192). The patients received an IV infusion dose of 0.6, 1.2, 1.8 or 2.4 mg/kg DM over 10 minutes. The PK parameters of DMA are summarized in the following table.

Parameter	Pediatric Patients Dose (IV)				Healthy Adult Volunteer Dose (IV)		
	0.6 mg/kg N=10	1.2 mg/kg N=12	1.8 mg/kg N=12	2.4 mg/kg N=12	0.64 mg/kg N=24	1.3 mg/kg N=24	2.5 mg/kg N=24
Cmax (ng/ml)	136 (24)	316 (34)	538 (54)	739 (53)	161 (29)	320 (25)	647 (29)
tmax (h)	0.41 (43)	0.52 (37)	0.47 (44)	0.61 (34)	0.62 (61)	0.62 (64)	0.67 (37)
AUC_{0-} (ng.h/ml)	451 (37)	949 (36)	1882 (53)	2731 (73)	910 (31)	1797 (28)	3638 (33)
$t_{1/2}$ (h)	4.8 (25)	4.6 (35)	5.0 (19)	5.1 (40)	6.6 (33)	7.3 (24)	7.7 (22)
CL_{app} (ml/min/kg)	18.8 (41)	17.2 (29)	14.3 (38)	14.7 (43)	9.31 (28)	9.39 (28)	9.48 (34)

Pediatric Surgery Patients:

The apparent oral clearance of DMA for pediatric surgery patients (2 to 12 years) was approximately 1.3 times greater compared to adult healthy volunteers and 2.0 times smaller compared to pediatric cancer patients (3 to 11 years). The apparent clearance of DMA for pediatric surgery patients (2 to 11 years) was approximately 1.4 times greater compared to adult healthy volunteers and 1.3 times smaller compared to pediatric cancer patients (3 to 11 years).

Oral Dose: The PK of DMA was studied in 11 children (2 to 12 year old) undergoing elective and uncomplicated surgery under general anesthesia following oral administration of 1.2 mg/kg dose of DM (study AN-PD-0993). The PK parameters of DMA are summarized in the following table.

IV Dose: The PK of DMA was studied in 18 children (2 to 11 year old) undergoing elective and uncomplicated surgery under general anesthesia following IV administration of 1.2 mg/kg dose of DM (study AN-PD-0593). The PK parameters of DMA are summarized in the following table.

Parameters	Mean (%CV)			
	Oral		IV	
	Pediatric Surgery Patients (2 to 12 yr, N=11)	Adult Healthy Volunteers (20 to 43 years, N=16)	Pediatric Surgery Patients (2 to 11 yr, N=18)	Adult Healthy Volunteers (19 to 40 years, N=24)
Dose	1.2 mg/kg	1.3 mg/kg	1.2 mg/kg	1.27 mg/kg
AUC_{0-} (ng.h/ml)	933 (61)	1181 (39)	1356.0 (42)	1797 (28)
Cmax (ng/ml)	159 (32)	225 (24)	254.6 (22)	320.0 (25)
tmax (h)	1.39 (70)	0.70 (30)	0.63 (57)	0.62 (64)
CLapp,po (ml/min/kg)	20.77 (49)	15.5 (35)	-	-
CLapp (ml/min/kg)	-	-	13.13 (47)	9.39 (28)
Vapp (L/kg)	-	-	5.17 (43)	5.77 (25)
t1/2 (h)	5.89 (24)	7.47 (21)	4.77 (23)	7.32 (24)

Pharmacokinetics in Special Populations:

· The pharmacokinetics of DMA is similar between male and female healthy volunteers and also similar between young (19 to 40 years) and elderly (≥65 years) healthy volunteers following both oral and intravenous administration of dolasetron mesylate.

Gender and age (19 to 87 years) has no effect on the apparent oral clearance and apparent clearance of DMA in cancer patients receiving chemotherapy.

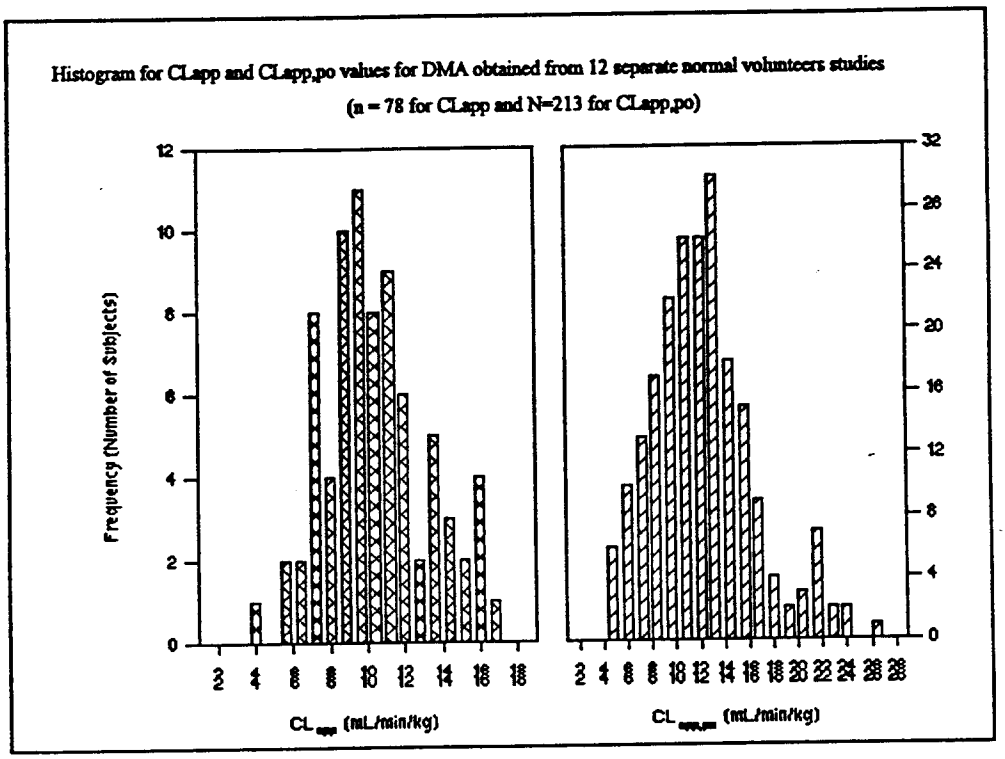
Mean (%CV) PK Parameters of DMA in Healthy Male, Female and Elderly (>65 yr) Subjects Following IV and Oral Administration of DM						
Parameters	IV			Oral		
	Male (N=24)	Female (N=24)	Elderly (N=15)	Male (N=24)	Female (N=24)	Elderly (N=15)
Dose	2.54 mg/kg	2.40 mg/kg	2.40 mg/kg	2.54 mg/kg	2.40 mg/kg	2.40 mg/kg
Cmax ng/ml	647 (29)	522 (18)	646.9 (29)	601 (35)	469 (19)	661.9 (28)
AUC_{0-} ng.h/ml	3638 (33)	3007 (34)	4028.1 (39)	2680 (30)	2413 (38)	3593.0 (42)
t1/2 h	7.66 (22)	8.05 (30)	6.85 (22)	8.84 (23)	9.11 (44)	7.16 (32)
Vapp L/kg	6.08 (30)	7.32 (36)	4.69 (23)	-	-	-
CLapp or CLapp,po ml/min/kg	9.48 (34)	11.1 (30)	8.26 (30)	12.9 (34)	14.2 (37)	9.53 (36)
CLr ml/min/kg	2.91 (25)	3.29 (41)	2.22 (37)	2.61 (28)	3.42 (62)	1.84 (24)
Urinary Exc (% dose)	32.8 (28)	33.4 (37)	27.9 (30)	21.6 (30)	27.2 (48)	21.4 (39)
F (%)	-	-	-	76 (28)	80 (12)	89 (16)

· The apparent oral clearance and apparent clearance of DMA decrease as renal function decreases. With severe renal impairment, the mean apparent oral clearance and apparent clearance of DMA decrease 44% and 48%, respectively, and the mean Cmax of DMA increases 17% (oral) and 34% (iv). Even though, the ranges of individual apparent oral clearance and apparent clearance values of DMA for renally impaired subjects are not considerably different from those observed in healthy normal volunteers, the range of Cmax of DMA for renally impaired subjects for IV administration is greater than those observed for healthy normals. Also, data for cardiac conduction changes showed that frequency of QTc prolongation beyond 440 msec was much higher in severe renal impaired group. The pharmacokinetic and safety results suggest that a dose adjustment may be necessary for renally impaired cancer or surgery patients (reduction of about 30%) .

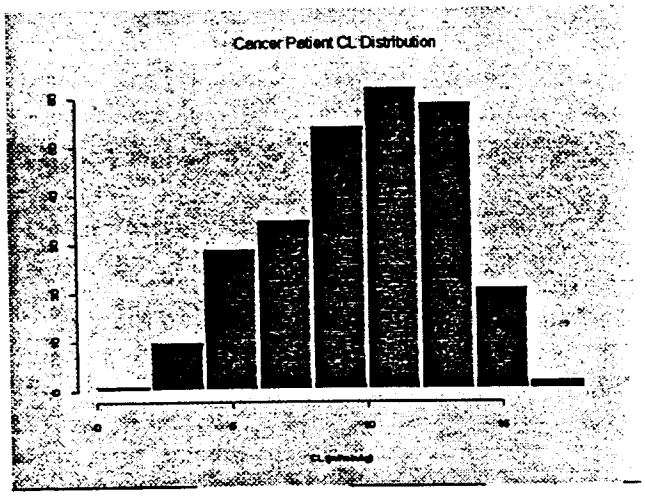
· The apparent oral clearance of DMA decreases as hepatic function decreases. Following oral administration of dolasetron mesylate, the mean apparent oral clearance of DMA decreases 42% and the mean AUC of DMA increases 70% with severe hepatic impairment. Also, with severe hepatic impairment, Cmax of DMA increased slightly, 18 % (oral), and was unchanged for IV group. However, the ranges of individual apparent oral clearance, AUC and Cmax of DMA for hepatically impaired subjects are not considerably different from those observed in healthy normal volunteers (note that each group had only 4 to 6 subjects). Following intravenous administration of dolasetron mesylate, the apparent clearance and AUC values of DMA remain relatively unchanged with hepatic impairment. Dose adjustment (reduction) may not be necessary for oral or IV treatment in hepatic impaired patients (safety parameters such as QTc interval prolongations were not evaluated).

· Following both oral and intravenous administration of dolasetron mesylate, the systemic exposure of DMA increases approximately two-fold in CYPIID6 deficient subjects while Cmax remains unchanged.

The incidence of adverse events observed in CYPIID6 deficient subjects did not differ from that observed in other normal subjects.



In spite of genetic polymorphism in CYPIID6, the apparent oral clearance and apparent clearance values of DMA exhibited a unimodal normal distribution pattern in normal subject as shown above (data pooled from all PK studies in normals) and in Cancer Patients (shown on the right). The safety and pharmacokinetic results suggest that dose adjustment may not be necessary for CYPIID6 deficient cancer or surgery patients.



Pharmacodynamics on ECG Changes:
Acute, reversible, and asymptomatic changes in PR interval and QRS duration observed after iv therapeutic doses of dolasetron mesylate, are directly related to plasma concentrations of DMA. The magnitude of these changes with plasma concentrations of DMA are small

;) indicating that small

changes in PR interval and QRS duration are expected with large changes in plasma concentrations of DMA and similar between healthy normal volunteers and cancer patients receiving chemotherapy. Patient demographics such as age, gender, race, body weight, body surface area, height and concomitant drugs such as doxorubicin, cyclophosphamide, verapamil, atenolol, nifedipine, glibenclamide, furosemide, diltiazem, propranolol, and ACE inhibitors had no effect on the PR interval and QRS duration changes.

Mean Slope and Maximum Observed and Predicted Values for PR Interval and QRS Duration Changes Following Oral and Intravenous Administration of Dolasetron Mesylate

Study and Dose	*Slope for Changes (msec/ng/mL)*		*Maximum PR Interval Changes (msec)*		*Maximum QRS Duration Changes (msec)*	
	PR interval (SD)	QRS duration (SD)	Observed	Predicted*	Observed**	Predicted*
Healthy Subjects						
MCPR0080 50, 100, 200 mg IV and 200 mg oral	0.0316 (0.0210)	0.0141 (0.0132)	19.8	15.8	7.9	6.5
Cancer Patient						
MCPR0032 0.6, 1.2, 1.8, 2.4, 3.0 mg/kg IV	0.0353	0.0139	16.6	18.1	6.9	6.8

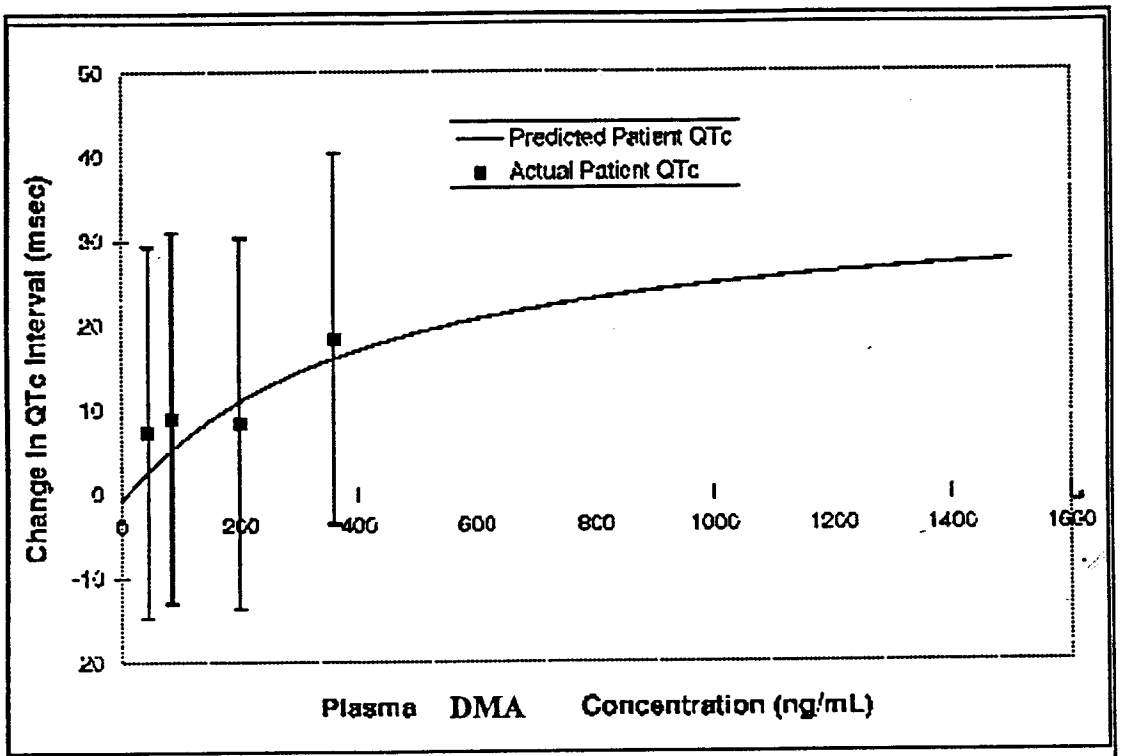
* Predicted values based on the linear model using the mean plasma concentration of DMA at which a maximum PR interval or QRS duration change was observed.

** Mean maximum observed changes after the highest dose in the study

Increases in QTc interval were significantly correlated with plasma concentrations of DMA, the relationship being non-linear with the rate of increases in QTc decreasing with increasing concentration. Cancer chemotherapy, particularly doxorubicin, contributed to the increases observed in patients. The increase was inversely related to baseline QTc. Review of data from outlier patients indicates large variability among acute QTc interval changes, plasma DMA levels and baseline QTc intervals.

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

The submitted PK-PD analysis were reviewed by the DPE-II with the assumption that QRS, PR and QT intervals were recorded/measured accurately. Also, most ECG recordings were carried out near the peak concentration of DMA (tmax). The paucity of PD data covering the entire corresponding concentration time profile is also a limitation of the submitted PK-PD analysis.



Predicted and Mean Observed Changes in QTc Interval for Cancer Patients Receiving Chemotherapy As a Function of Mean Maximal Plasma DMA Concentrations Observed Following 25, 50, 100 and 200 mg IV and Oral Doses

Even though probability of prolongation in ventricular repolarization is less with DM and it is acknowledged that there were no instances of Torsades des pointes reported in clinical trials, prolongation of QTc interval raises questions about the 'practicality of use' of this drug. For instance, giving a second or a third dose of DM to treat vomiting (as is possible for DM Injection) will increase the risk for QTc prolongation and possibly the risk of Torsades des pointes. This risk is even greater for patients with reduced clearance of the active metabolite, viz. renal impairment.

Drug-Drug Interactions: The potential for clinically significant drug-drug interactions in the elimination of dolasetron and DMA appears to be minimal since the reduction of dolasetron to DMA is complete and stable due to the ubiquitous nature of the mediating enzyme (carbonyl reductase) and DMA is eliminated by multiple routes (renal excretion and metabolism by hydroxylation and glucuronide conjugation). The potential of DMA to affect elimination of other drugs has not been studied. However, the potential for DMA to inhibit in vivo metabolism of CYPIID6 and CYPIIIA substrates appears to be minimal since the in vitro inhibition constants (Ki) of DMA for CYPIID6 and CYPIIIA mediated metabolism (30 μM

and 674 μM, respectively) are much greater than plasma concentrations of DMA observed after therapeutic doses of dolasetron mesylate.

The drug-drug interaction potential for dolasetron mesylate was evaluated as follows:

1. Cimetidine and Rifampin: Formal drug-drug interaction studies in normal volunteers were conducted using a nonspecific P450 inhibitor, cimetidine, and a classic P450 enzyme inducer, rifampin, to describe the magnitude of an interaction involving oxidative metabolism of DMA.

Mean (%CV) Steady-State PK Parameters of DMA Obtained Following Once Daily Oral Administration of DM (200 mg/day) Alone, with Cimetidine (1200 mg/day), and with Rifampin (600 mg/day) for 7 Days

PK Parameters	Mean (%CV)		
	DM alone (N=18)	DM with Cimetidine (N=18)	DM with Rifampin (N=17)
AUCss (ng.h/ml)	3654 (31)	4551 (33)	2682 (31)
Cmaxss (ng/ml)	732.7 (24)	842.2 (31)	614.3 (23)
tmax (h)	0.67 (29)	0.78 (10)	0.82 (18)
t1/2 (h)	8.8 (19)	8.4 (18)	7.4 (20)
CLapp,po (ml/min/kg)	10.5 (29)	8.4 (28)	14.4 (30)
Urinary Exc. (% dose)	21.7 (47)	25.2 (37)	19.8 (52)

2. Concomitant Medications in Cancer Patients: Population pharmacokinetics, when practical, were examined to determine whether concomitant medications in clinical databases are significant covariates that affect pharmacokinetics of DMA in the target population. When investigated in 273 cisplatin- treated cancer patients participating in a multicenter safety and efficacy trial by a covariate analysis of population PK modeling, of the concomitant medications tested, atenolol was found to be a significant covariate affecting the apparent clearance of DMA. The mean apparent clearance for DMA for patients on atenolol decreased by 27 % compared to patients not on atenolol. A possible mechanism for this interaction could be the inhibition in the active secretion of DMA by the kidney since atenolol also appears to be actively secreted by the kidney[1]. However, apparent clearance values of DMA for patients on atenolol were well within the values observed in patients not on atenolol) therefore this interaction may not be of much clinical importance. Other concomitant medications such as furosemide, nifedipine, diltiazem, ACE inhibitors, verapamil, glibenclamide and propranolol had no effect on the apparent clearance of DMA.

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1 Boyd, R A ; Chin, S K; Dn-Pedro O; Williams, R L; Giacomin, K M; Clin. Pharmacol. Ther. 1989 48: 403-410

Comparison of Human PK to Animals:

The overall biotransformation pathways of DM are identical in animals (rat, dog and monkey) and man. Qualitatively, the PK of DM and the metabolite, DMA, in animals and man appear to be similar. The mass balance breakdown of ^{14}C-DM in different species was similar (Urine, Feces and Total).

Mean PK Parameters for DM and DMA after IV Administration of DM				
DM				
Parameters	Rat	Dog	Monkey	Healthy Subjects (N=5)
WT (kg)	0.269	12.1	6.20	74.3
Dose (mg/kg)	15.0	6.0	5.0	5.0
CL (ml/min/kg)	189	187	402.9	95.8
Vd (L/kg)	1.1	1.2	5.56	5.39
t1/2 (min)	6.6	6	9	151
AUC (ng.h/ml)	978	401	173	660
DMA				
Cmax (ng/ml)	668	677	756	1926
tmax (h)	0.25	0.31	0.08	0.56
CLapp (ml/min/kg)	180	19.6	57.4	7.76
Vdapp (L/kg)	10.06	104.74	139.66	529.15
t1/2 (h)	2.4	5.1	4.23	10.88
AUC (ng.h/ml)	1035	3883	1098	7993

In following table, the two-hour plasma DM and DMA concentrations measured in animals during toxicity studies are compared to those observed in healthy subjects and cancer patients after administration of the highest dose of dolasetron mesylate.

Comparison of 2 Hour Plasma Concentration (Mean ± SD) after Administration of DM				
Species	Route	Dose (mg/kg/day)	2-Hour Plasma Concentration (ng/ml)	
			DM	DMA
Rat	IV po	60.0 100.0	3302 91 ± 51	2860 1437 ± 432
Dog	IV	6.0	< 10	524
Monkey	IV po	5.0 50.0	< 10	122 ± 30 351 ± 120

Healthy Subjects	IV po	5.0 5.0	25 ± 5.6	1085 ± 240 643 ± 123
Cancer Patients	IV po	3.0 2.8	_ _	412 ± 200 494 ± 356

In rats, after iv administration of 60 mg/kg/day dose of dolasetron mesylate, some rats died due to convulsions, while at 100 mg/kg/day oral dose was free of significant toxic effects. In dogs, at 6.0 mg/kg/day iv dose of dolasetron mesylate, emesis was noted in male dogs, while in monkeys, after oral and iv administration of 50 mg/kg and 5 mg/kg dose of dolasetron mesylate, respectively, no treatment-related clinical signs were observed. The two-hour plasma dolasetron concentration was much lower in dog, monkey, and man compared to rat due to the rapid disappearance of dolasetron from plasma. The two-hour plasma DMA concentration in healthy subjects and cancer patients was either similar or lower than those observed rats and dogs.

In-vitro Dissolution: The following table summarizes the in vitro dissolution performance of formulation used in pivotal phase III trial and formulation proposed for marketing (200 mg). The sponsor is proposing to market 50 mg and 200 mg tablet strengths which are compositionally proportional. The lots sizes were adequately representative of production lot sizes. The dissolution was carried out using USP paddle apparatus at 50 rpm and in 0.1 N HCL (900 ml) at 37.0 ± 0.5 °C.

Lot #	Times	N	Mean	Low	High	% CV
C-51610 Phase III Formulation	15 min 30 min 45 min	12 12 12	97 % 99 % 99 %	89 % 98 % 98 %	99 % 100 % 100 %	3 % 1 % 1 %
R-54062 Proposed Market Formulation	10 min 20 min 30 min	12 12 12	53 % 99 % 100 %	37 % 95 % 100 %	84 % 100 % 100 %	30 % 2 % 0.7 %

Comments:

A.

1.

2.

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7.

B. (to be sent to Sponsor)

1. The Division of Pharmaceutical Evaluation II, OCPB would recommend a dissolution specification

2. In the bioequivalence study MCPR0089, the batch size of to-be-marketed 200 mg tablet was

C. (Labelling Comments)

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DRAFT LABELING

1. The proposed table under "Pharmacokinetics in Humans (po)" should include variability on CLapp/F and $t_{1/2}$ parameters (e.g. % CV).

2. The proposed table under "Pharmacokinetics in Humans (iv)" should include variability on CLapp/F and $t_{1/2}$ parameters (e.g. % CV).

3. Under "Pharmacokinetics in Humans" the sponsor should include a variability (e.g. %CV) on volume of distribution.

4. Under "Clinical Studies (po)" section, the sponsor should state the following for PONV indication: "Men have not been clinically studied to establish efficacy".

5. The sponsor states in (iv) labelling: "the distribution of MDL 74,156 to blood cells is not extensive". However, partitioning of ^{14}C-radioactivity in plasma versus blood was studied. Sponsor is requested to clarify whether including MDL 74,156 in place of ^{14}C-radioactivity in this statement is appropriate.

Appendix I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020623

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Tablet Formulation

The following table describes the formulations for dolasetron tablet. These are the strengths tested in different clinical pharmacology trials in phase III. There is no difference in formulation between phase III-tablet and to-be-marketed tablet It should be noted that only 50 mg and 200 mg strengths are proposed by the sponsor for marketing and they are compositionally proportional.

Composition of Dolasetron Mesylate Tablet (mg)	Tablets Theoretical Quantity per			
Component	25 mg Tablet	50 mg Tablet	100 mg Tablet	200 mg Tablet
Dolasetron Mesylate Monohydrate				
Croscarmellose Sodium				
Lactose				
Magnesium Stearate				
Pregelatinized Starch				
Total Tablet Weight				

All tablet sizes and shapes are the same for phase III and commercial tablets. The 25 and 50 mg are standard round concave tablets. The 100 and 200 mg are capsule shaped tablets for ease of swallowing. All tablet strengths for Phase III clinical studies were

There is no difference between phase III and commercial formulations for the 25 mg tablets. The commercial formulations for the other three strengths contain different amounts of red iron oxide in the . The 50 mg tablets are light pink, the 100 mg tablets are pink and the 200 mg tablets are dark rose (dark pink, mauve).

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In vitro metabolism/DMA Inhibition of dextrorphan and 1'hydroxymidazolam Formation

Objective: The study was designed to evaluate the potential for DM to interact with CYP2D6 and CYP3A substrates (dextromethorphan and midazolam respectively) using in vitro human liver microsome studies

Summary: DMA is a potent 5-HT3 receptor antagonist and has been shown to be metabolised by CYP2D6, CYP3A and FMO. The effect of DMA on dextrorphan formation and 1'hydroxymidazolam formation was assessed in three human livers. The CYP2D6 mediated O-demethylation of dextromethorphan was competitively inhibited by DMA with Ki ranging from The in vivo inhibition of CYP2D mediated biotransformation should be unlikely as the therapeutic concentration of DMA is much below 17 µM. Likewise, DMA was found to non-competively inhibit the 1'-hyroxylation of midazolam with a Ki ranging from µM. Thus, the potential for DMA to inhibit the in vivo metabolism of CYP3A substrates appears to be minimal.

Figure 1A. *Dextrorphan Formation in the Presence of MDL 74,156 In a Human Liver Microsomal Sample (IUL-3)*

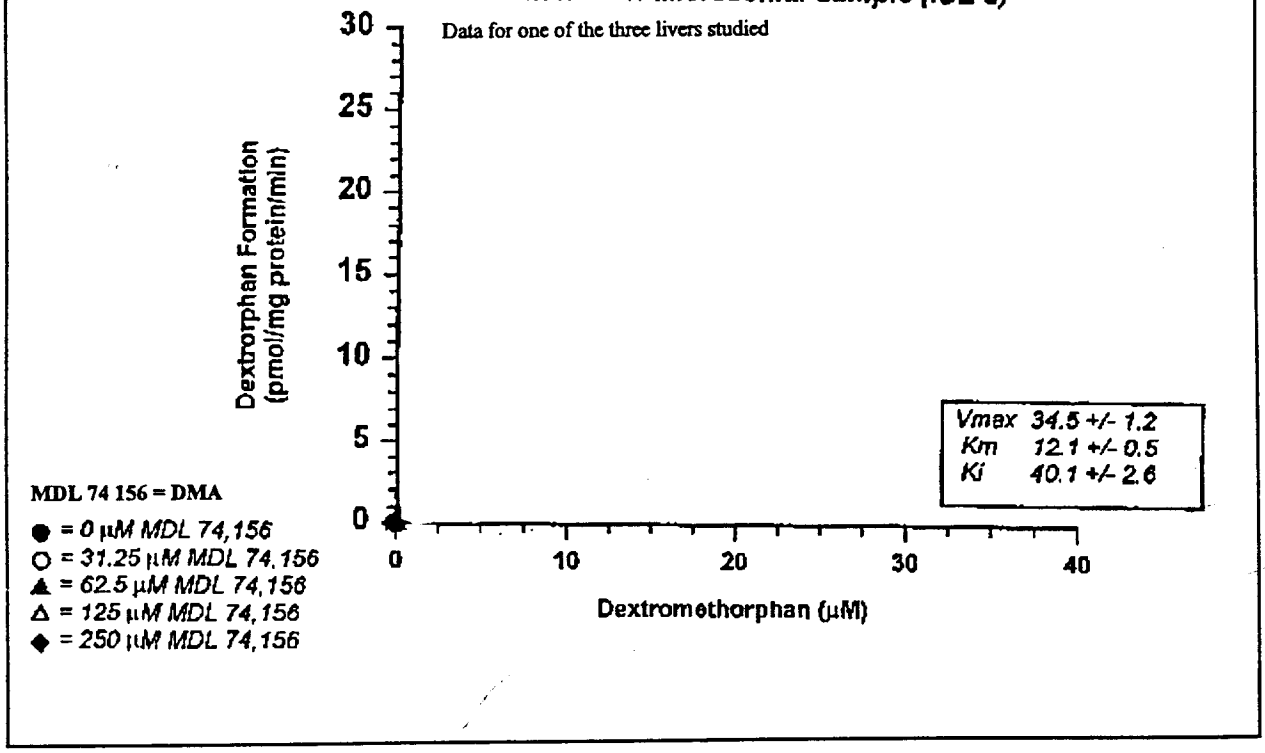
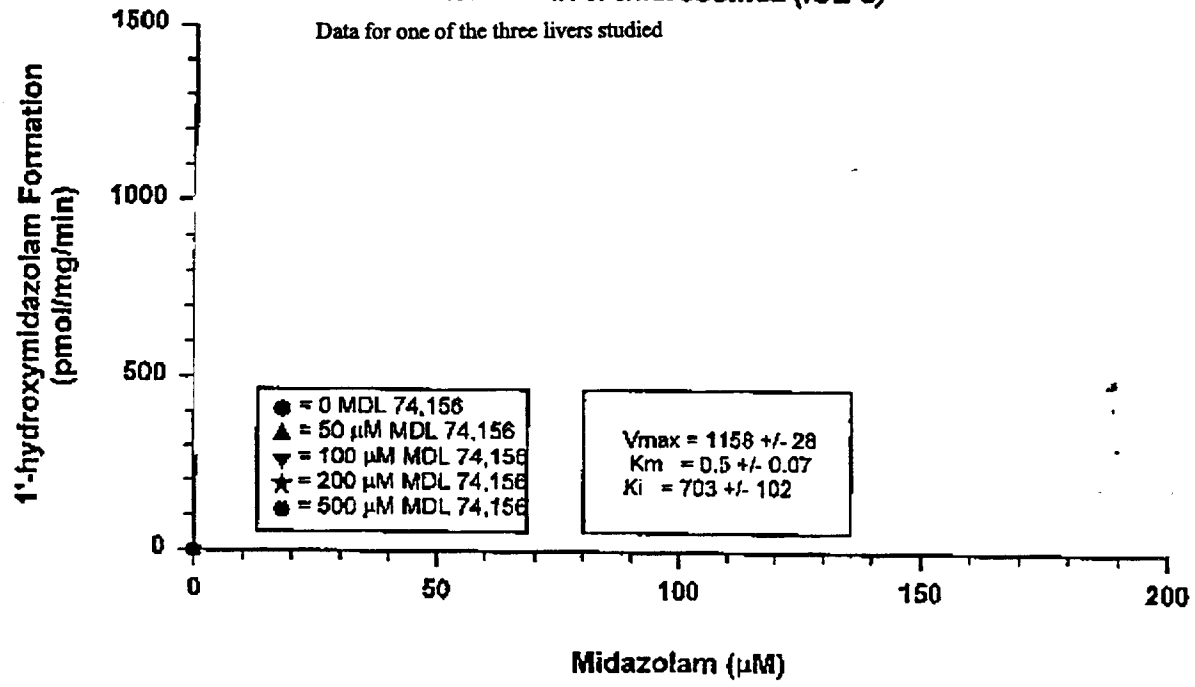


Figure 2A. *Inhibition of 1-hydroxymidazolam formation by MDL 74,156 in human liver microsomes (IUL-3)*



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Pharmacokinetics and Metabolism of Dolasetron (DM) Following Oral Administration of ^{14}C-DM

Protocol Number: 73147-1-C-029

Objectives:

To investigate the disposition of DM and its reduced metabolite, DMA
To determine total recovery of the administered dose
To identify and profile urinary metabolites of DM following a single IV dose of ^{14}C-DM to normal volunteers.

Formulation: The following table presents a 10 mg/ml oral ^{14}C-DM solution used in the study.

Batch No	C-49128
Site of Manufacturing	
Date of Manufacturing	11-29-90
Dosage Form	Injectable Solution
Strength	10 mg/ml
Specific Activity	5 μCi/ml
Batch Size	
	10 ml solution in ampule

Study Design and Sampling:

This was an open-label, single dose fashion with six healthy non-smoking male volunteers between) years of age. Each subject received a single oral dose of 300 mg ^{14}C-DM (100 μCi). Serial blood, urine and fecal samples were collected until the radioactivity of the last two samples was less than two times background radioactivity.

Data Analysis:

Pharmacokinetic parameters were calculated from plasma and urine concentration-time data by model independent methods and total mass recovery was determined from urinary and fecal elimination of ^{14}C-radioactivity.

Results:

The recovery of ^{14}C-radioactivity, DM and DMA is shown in the following table. The mean plasma concentration-time plots and pharmacokinetic parameters for ^{14}C-radioactivity, DM and DMA are presented in Figure 1 and Table 2.

Table 1 Excretion of ^{14}C-radioactivity, DM and DMA following oral administration of 300 mg ^{14}C-DM (N = 6)

	Percent of Dose (%)*		
	Urine	Feces	Total
^{14}C-radioactivity	58.6 ± 10.4	25.3 ± 9.2	83.9 ± 7.6
DM	ND		
DMA	30.1 ± 14.5		

ND Not detected
* Mean ± SD

Figure 1 Mean plasma concentration versus time plots for ^{14}C-radioactivity, DM and DMA following single oral administration of 300 mg ^{14}C-DM (N = 6)

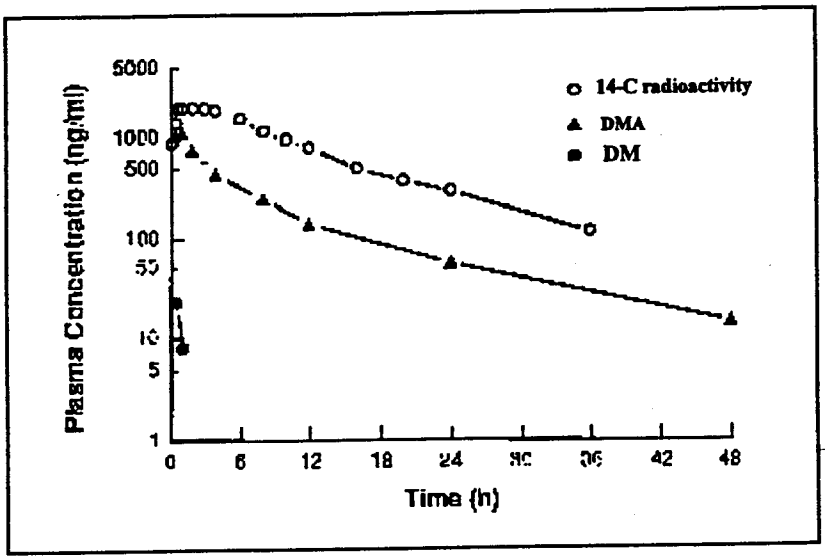


Table 2 Mean (%CV) pharmacokinetic parameters for ^{14}C-radioactivity, DM and DMA

	14-C radioactivity (%cv)	DMA (%cv)
AUC_{0-} (ngeq or ng.h/ml)	26027 (15)	6854 (46)
Cmax (ngeg/ml or ng/ml)	2119 (13)	1197 (28)
tmax (h)	1.52 (76)	0.77 (34)
CLapp,po (ml/min/kg)	2.76 (12)	9.10 (42)
K*	0.86 (8)	NA
CLr (ml/min/kg)	1.60 (13)	2.31 (11)
AUC_{0-} ratio (%)**	NA	34.8 (40)

NA: Not applicable
* : Blood to plasma concentration ratio of 14-C radioactivity
** : AUC_{0-} ratio of DMA to 14-C radioactivity calculated based on molar equivalent concentrations

Approximately 84 % of the intravenously administered ^{14}C-radioactivity was recovered in urine (58.6 %) and feces (25.3 %) in 4 days after dosing. No quantifiable amount of DM was excreted in urine, suggesting that DM is extensively metabolised. About 30 % of the dose was excreted in urine as DMA.

More than 98 % of urinary ^{14}C-radioactivity was identified. These included DMA (60.9 %), 5' OH-DMA (3.4 %), 6' OH-DMA (6.7 %) and the conjugates of DMA, 5'OH-DMA and 6'OH-DMA (28.1 %). The existence of the N-oxide of DMA was also evident (1.0 %), although it represents a very minor part of the overall metabolism of DM. The conjugates consisted of DM glucuronide (17.2 %), 5' OH-DMA glucuronide (5.6 %), 6' OH-DMA glucuronide (2.0 %), 6' OH-DMA sulfate (1.3 %) and unidentified conjugates (2.0 %). The majority (> 85 %) of urinary DMA was excreted as a R(+)-enetiomer. The profiling results of urinary metabolites were similar to those observed after an iv dose.

Conclusions:

Renal excretion was the major route for the intravenously administered ^{14}C-radioactivity. DM is rapidly and extensively metabolized. DMA was eliminated by multiple routes (i.e. excretion, hydroxylation, glucuronide conjugation and N-oxidation) with t1/2 of about 7 hours. The N-oxidation of DMA was a very minor elimination pathway compared to other routes. DMA was the major metabolite, representing 35 % and 61 % of ^{14}C-radioactivity in plasma and urine, respectively.

Pharmacokinetics and Metabolism of Dolasetron (DM) Following Intravenous Administration of ^{14}C-DM

Protocol Number: 73147-1-C-011

Objectives:

To investigate the disposition of DM and its reduced metabolite, DMA
To determine total recovery of the administered dose
To identify and profile urinary metabolites of DM following a single IV dose of ^{14}C-DM to normal volunteers.

Formulation: The following table presents a 10 mg/ml injection ^{14}C-DM solution used in the study.

Batch No	IC-4435
Site of Manufacturing	
Date of Manufacturing	11-29-90
Dosage Form	Injectable Solution
Strength	10 mg/ml
Specific Activity	5 µCi/ml
Batch Size	
	10 ml solution in ampule

Study Design and Sampling:

This was an open-label, single dose fashion with six healthy non-smoking male volunteers between years of age. Each subject received a single dose of 100 mg ^{14}C-DM (51 µCi) by intravenous infusion over 6 to 7 minutes. Serial blood, urine and fecal samples were collected until the radioactivity of the last two samples was less than two times background radioactivity.

Data Analysis:

Pharmacokinetic parameters were calculated from plasma and urine concentration-time data by model independent methods and total mass recovery was determined from urinary and fecal elimination of ^{14}C-radioactivity.

Results:

The recovery of ^{14}C-radioactivity, DM and DMA is shown in the following table. The mean plasma concentration-time plots and pharmacokinetic parameters for ^{14}C-radioactivity, DM and DMA are presented in Figure 1 and Table 2.

Table 1 Excretion of ^{14}C-radioactivity, DM and DMA following intravenous administration of 100 mg ^{14}C-DM (N = 6)

	Percent of Dose (%)*		
	Urine	Feces	Total
^{14}C-radioactivity	65.3 ± 6.6	16.2 ± 5.5	81.5 ± 11.1
DM	ND		
DMA	19.7 ± 2.6		

ND Not detected * Mean ± SD

Figure 1 Mean plasma concentration versus time plots for ^{14}C-radioactivity, DM (MDL 73, 147) and DMA (MDL 74,156) following single intravenous administration of 100 mg ^{14}C-DM (N = 6)

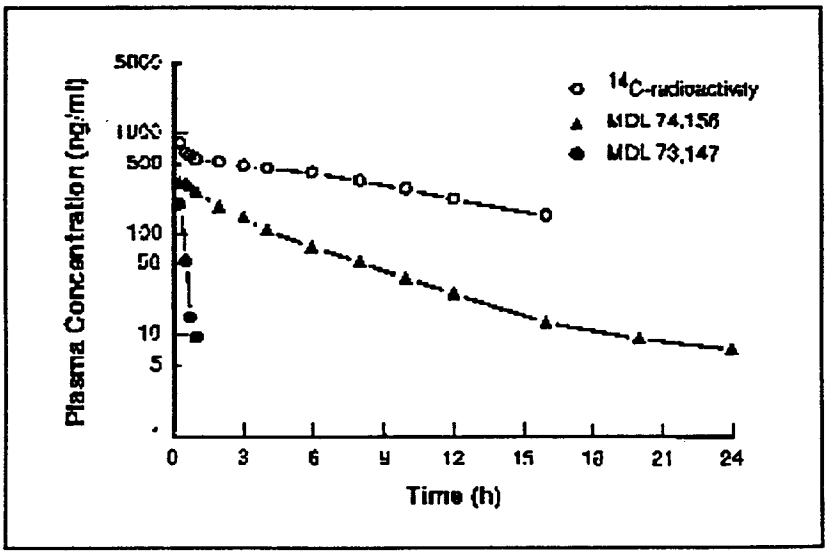


Table 2 Mean (%CV) pharmacokinetic parameters for ^{14}C-radioactivity, DM and DMA

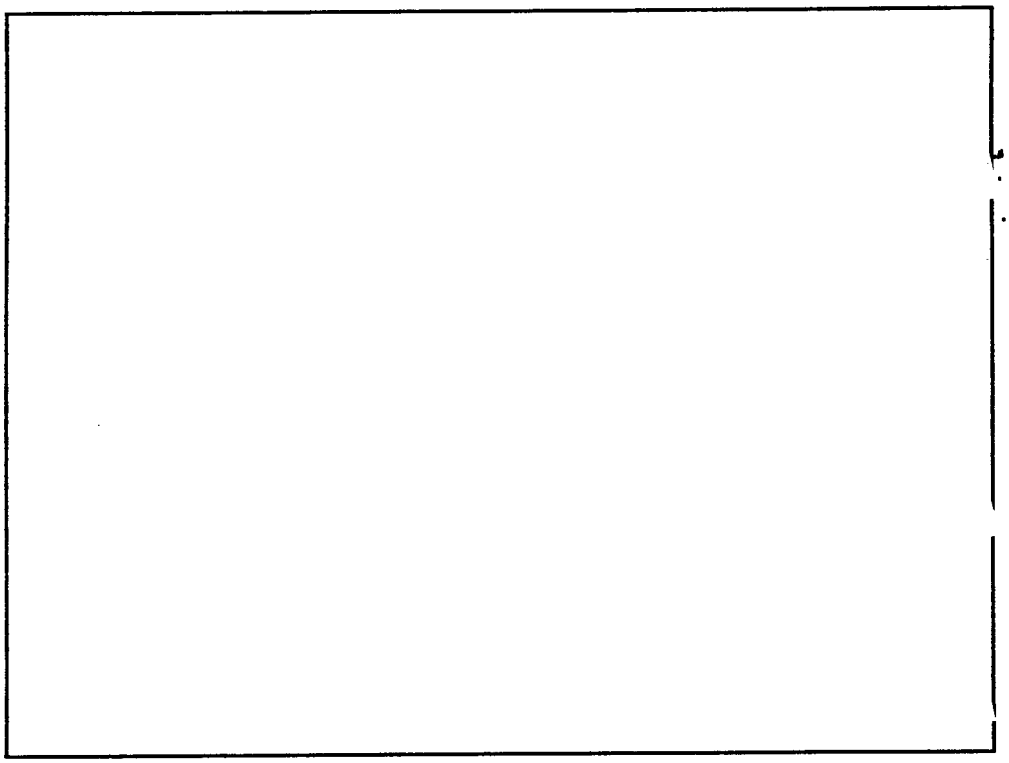
	14-C radioactivity (%cv)	DM (%cv)	DMA (%cv)
AUC_{0-} (ngeq or ng.h/ml)	7668.7 (8)	124.9 (21)	1447.5 (10)
Cmax (ngeg/ml or ng/ml)	NA	NA	367.2 (29)
tmax (h)	NA	NA	0.46 (54)
CL (ml/min/kg)	2.96 (13)	136.3 (11)	NA
V (L/kg)	2.40 (22)	1.47 (26)	NA
K*	1.07 (10)	NA	NA
CLr (ml/min/kg)	NA	ND	2.20 (14)
AUC_{0-} ratio (%)**	NA	2.21 (22)	25.6 (12)

NA: Not applicable
* : Blood to plasma concentration ratio of 14-C radioactivity
** : AUC_{0-} ratio of DMA to 14-C radioactivity calculated based on molar equivalent concentrations

Approximately 82 % of the intravenously administered ^{14}C-radioactivity was recovered in urine (65.3 %) and feces (16.2 %) in 4 days after dosing. No quantifiable amount of DM was excreted in urine, suggesting that DM is extensively metabolised. About 20 % of the dose was excreted in urine as DMA. The mean blood to plasma concentration ratio of ^{14}C-radioactivity was 1.07,

indicating the even distribution of radioactivity between plasma and blood cells.

More than 97 % of urinary ^{14}C-radioactivity was identified. These included DMA (53 %), 5' OH-DMA (5.1 %), 6' OH-DMA (13.2 %) and the conjugates of DMA, 5'OH-DMA and 6'OH-DMA (26.1 %). The existence of the N-oxide of DMA was also evident, although it represents a very minor part of the overall metabolism of DM. The majority (> 85 %) of urinary DMA was excreted as a R(+)-enetiomer.



Conclusions:

Renal excretion was the major route for the intravenously administered ^{14}C-radioactivity. DM is rapidly and extensively metabolized. Plasma AUC_{0-} of DMA was approximately 12 times greater than that of DM. DMA was the major metabolite, representing 26 % and 53 % of ^{14}C-radioactivity in plasma and urine, respectively.

Bioavailability of Production DM Tablet Administered to Normals Under Fed and Fasting Conditions

Study # MCPR0089

Objectives:

1. Determine the bioequivalence (BE) of the proposed final marketed dolasetron tablet as compared to the phase III dolasetron tablet
2. Characterize the effect of a high fat meal on the apparent oral bioavailability of the proposed fianl marketed DM tablet
3. Determine the apparent oral bioavailability of a prototype phase III DM tablet and proposed final marketed DM tablet as compared to a DM oral reference solution

Formulation:

The manufacturing history of the 10 mg/ml injectable solution (used orally in the solution reference treatment), phase III 200 mg tablets, and proposed marketed DM tablets used in the study are presented in following tables.

Batch No	C-49127
Site of Manufacturing	
Date of Manufacturing	10-15-91
Dosage Form	Injectable Solution
Strength	10 mg/ml
Batch Size	
Comments	Pilot lot

Batch No	C-51610
Site of Manufacturing	
Date of Manufacturing	10-05-92
Dosage Form	Tablet
Strength	200 mg
Batch Size	
Comments	prototype phase III DM tablet

Batch No	R54062
Site of Manufacturing	
Date of Manufacturing	01-18-94
Dosage Form	Tablet
Strength	200 mg
Batch Size	
Comments	Proposed marketed final formulation

Study Design:
The study was conducted in an open-label, randomized, four-way cross-over design with 24 healthy subjects (males), between ages of years. Subjects received one of the following treatment in each period:

Treatment A: 200 mg DM in oral reference solution given to fasting subjects as a single oral dose
Treatment B: One prototype phase III 200 mg DM tablet given to fasting subjects as a single oral dose
Treatment C: One 200 mg proposed marketed DM tablet given to fasting subjects as a single dose
Treatment D: One 200 mg proposed marketed DM tablet given to subjects (8:00 am) with a high fat breakfast (served at 7:30 am) as a single dose

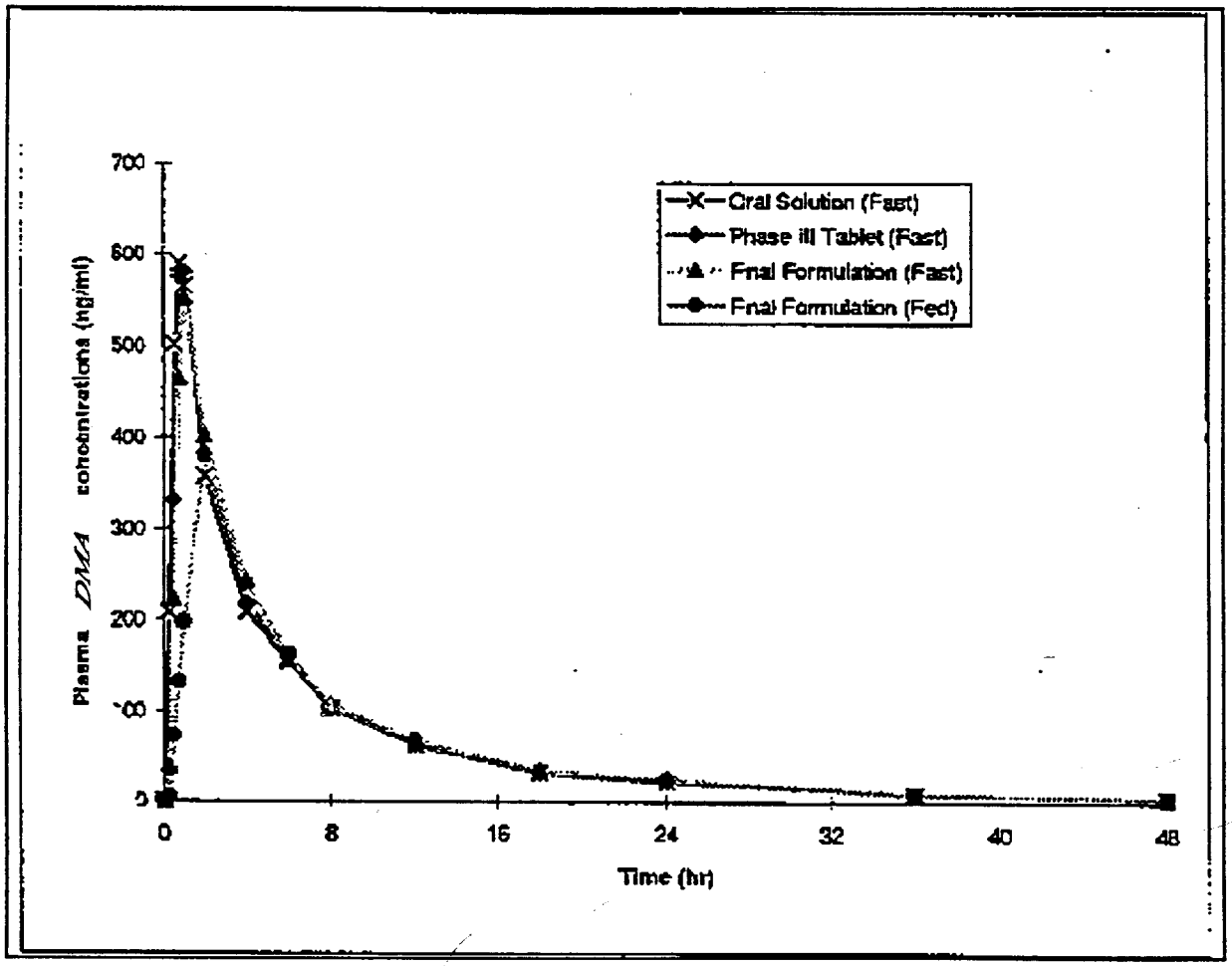
A six day drug free interval (washout period) was included between treatments. Serial plasma samples were collected for 48 hours after dosing.

Standard Meal Content: 2 eggs fried in butter, 2 strips of bacon, 2 pieces of buttered toast, 2 oz hashbrowns and 8 oz whole milk. The meal has 55 g fat, 33 g protein and 58 g carbohydrate.

Data Analysis: Pharmacokinetic parameters for DMA were calculated from plasma concentration-time data by model independent methods.
Statistics: To compare the treatment groups, the log-transformed data were analyzed with an analysis of variance, with terms for subject, period and treatment. It was noted that in this study 23 subjects were assigned to four treatments in 23 different sequences. Therefore, sequence and subject-in-sequence terms were not used in the ANOVA model.

Results: Figure 1 presents mean plasma concentration-time plots for DMA obtained following oral administration of 200 mg DM. Mean pharmacokinetic parameters for DMA are summarized in the following table.

Figure 1



Mean (%CV) Plasma Pharmacokinetic Parameters for DMA

Variable	TRT	Mean	(%CV)
$AUC_{(0-\infty)}$ (ng.h/ml)	A	3120	34
	B	3119	31
	C	3210	35
	D	2797	36
Cmax (ng/ml)	A	659.2	23
	B	650.3	30
	C	597.8	21
	D	439.0	37
tmax (hr)	A	0.74	28
	B	0.88	15
	C	1.24	60
	D	1.95	40
CLapp.po (ml/min/kg)	A	10.8	32
	B	10.6	29
	C	10.5	32
	D	12.4	40
t1/2 (hr)	A	8.24	19
	B	8.19	22
	C	8.19	21
	D	8.29	24
Bioavailability (%) Determined by comparing the mean of the ratios of plasma $AUC_{(0-\infty)}$ of DMA	B/A	101.2	11
	C/A	103.5	13
	C/B	102.7	12
	D/A	90.1	18
	D/C	87.2	15

BE Results: The following table shows the BE results for treatment C vs B, (point estimates and 90% confidence intervals) for log-transformed analysis.

Parameters	Point estimate	90 % Confidence intervals
$AUC_{(0-\infty)}$	101.9	96.6 - 107.5
Cmax	93.6	83.4 - 105.0

The following table shows the BE results for treatment C vs A, (point estimates and 90% confidence intervals) for log-transformed analysis.

Parameters	Point estimate	90 % Confidence intervals
$AUC_{(0-\infty)}$	102.3	97.0 - 107.3
Cmax	90.4	81.1 - 101.0

Conclusions:

1. Both the prototype phase III 200 mg DM tablet and proposed final marketed DM tablet showed 100% bioavailability compared to the oral reference solution
2. The proposed, final, marketed DM tablet is bioequivalent to the prototype phase III 200 mg DM tablet utilized in clinical trials
3. The proposed, final, marketed DM tablet is bioequivalent to 200 mg DM in oral reference solution (same as injectable solution) given to fasting subjects as a single oral dose.
4. When proposed marketed dolasetron tablet was given with a high fat meal DMA $AUC_{(0-\infty)}$ decreased by 12.5% and DMA Cmax decreased by 26%
5. Tmax of the to-be-marketed formulation showed greater variability than the phase III clinical trial formulation

Bioavailability of Dolasetron Tablets Compared to an Intravenous Infusion and an Oral Solution

Study: MCPR0035

Objectives:
To determine the relative bioavailability of the dolasetron prototype tablet compared to an oral solution, to determine the absolute oral bioavailability of dolasetron, to assess the intrasubject variability of dolasetron pharmacokinetics and study the pharmacokinetics of dolasetron metabolites DMA, 5'OH-DMA and 6'OH-DMA after intravenous and oral administration of DM.

Formulation:

	Injectable Solution	Prototype Tablet
Batch No.	C-49127	C-51610
Site of Manufacturing		
Date of Manufacturing	10-15-91	09-17-92
Dosage Form	Injectable Solution	Tablet
Strength	10 mg/ml	200 mg
Batch Size		
Comments	Pilot Lot	Pilot Prototype Lot

Study Design: The study was conducted in an open-label, randomized, four-way cross fashion with 24 healthy, male subjects between the ages of years. Subjects received each of the following treatments on separate occasions. Additionally, subjects randomly received one of the treatments a second time. Therefore, each treatment was given 32 times to 24 subjects.

Treatment A: 200 mg DM in solution given by single 10 minute iv infusion.
Treatment B: Once 200 mg DM tablet given as a single oral dose.
Treatment C: 200 mg delasetron mesylate in solution given as a single oral dose.

Serial plasma and urine samples were collected up to 48 hr after dosing.

DATA ANALYSIS:

Pharmacokinetic parameters for each analyte were calculated from its plasma and urine concentration-time data by model independent methods. Estimated pharmacokinetic parameters include area under the plasma concentration-time curve from time 0 to infinity ($AUC_{(0-\infty)}$), maximum plasma concentration (C_{max}), time to maximum plasma concentration (tmax), terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL_{app}), renal clearance (CL_r), apparent volume of distribution during terminal phase (Vd_{app}), and percent of the dose excreted in urine.

PHARMACOKINETIC RESULTS:

Figure 1 presents the mean plasma concentration-time plot for DMA, obtained following iv and oral administration of 200 mg dolasetron mesylate. Mean pharmacokinetic parameters for metabolites are summarized in the following tables.

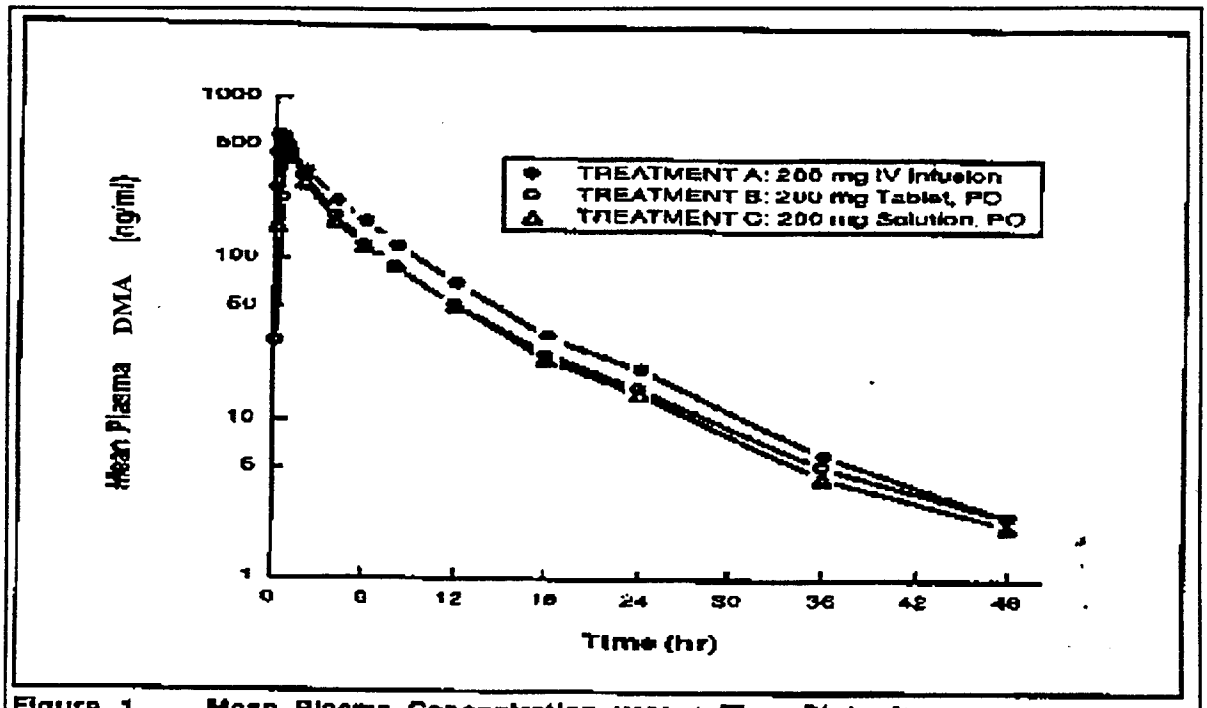


Figure 1. Mean Plasma Concentration versus Time Plots for DMA (N=31 for Treatments A and C and N=30 for Treatment B).

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Mean Pharmacokinetic Parameters of Treatments for DMA; TRT A: IV Infusion (N=31), B: Oral Tablet (N =30), C: Oral Solution (N= 31)

Variable	TRT	Mean	(%CV)
$AUC_{(0-\infty)}$ (ng.hr/ml)	A	3317	28
	C	2504	30
	B	2535	30
Cmax (ng/ml)	A	619.9	24
	C	555.9	28
	B	552.8	33
tmax (hr)	A	0.57	34
	C	0.77	21
	B	0.97	39
CLapp (ml/min/kg)	A	10.0	29
CLapp.po (ml/min/kg)	C	13.3	30
	B	13.4	29
$t_{1/2}$ (hr)	A	7.28	16
	C	8.25	18
	B	8.13	18
Vdapp (L/kg)	A	6.21	25
CLr (ml/min/kg)	A	2.95	31
	C	2.86	30
	B	2.90	48
Bioavailability	B/C	103.7	19
	C/A	72.3	17
	B/A	73.6	13

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Mean Pharmacokinetic Parameters of Treatments for 5' OH-DMA; TRT A: IV Infusion (N=31), B: Oral Tablet (N =30), C: Oral Solution (N= 31)

Variable	TRT	Mean	(%CV)
$AUC_{(0-)}$ (ng.hr/ml)	A	423.0	35
	C	414.7	34
	B	395.2	37
Cmax (ng/ml)	A	45.7	46
	C	43.8	40
	B	40.1	43
tmax (hr)	A	1.16	37
	C	1.33	53
	B	1.60	31
t1/2 (hr)	A	8.79	36
	C	8.25	40
	B	8.75	44
CLr (ml/min/kg)	A	2.08	31
	C	2.18	34
	B	2.31	40

Mean Pharmacokinetic Parameters of Treatments for 6' OH-DMA; TRT A: IV Infusion (N=31), B: Oral Tablet (N =30), C: Oral Solution (N= 31)

Variable	TRT	Mean	(%CV)
$AUC_{(0-)}$ (ng.hr/ml)	A	726.1	25
	C	687.6	23
	B	670.9	26
Cmax (ng/ml)	A	63.1	35
	C	62.3	32

	B	60.1	35
tmax (hr)	A	1.55	70
	C	1.59	52
	B	2.10	47
t1/2 (hr)	A	8.41	18
	C	7.78	21
	B	7.77	23
CLr (ml/min/kg)	A	3.14	25
	C	3.26	30
	B	3.38	36

The following table shows the mean percent of dose excreted in urine.

Mean (%CV) Percent of the Dose Excreted in Urine for 0-48 hour, TRT-A iv infusion (N=31), B- oral tablet (N=30), C- oral solution (N=31)

	TRT A	TRT C	TRT B
DM	ND	ND	ND
DMA	30.1 (26)	22.5 (32)	22.0 (36)
R(+)-DMA	26.8 (27)	19.7 (32)	19.2 (36)
S(-)-DMA	3.27 (22)	2.80 (31)	2.80 (40)
5'OH-DMA	2.60 (34)	2.67 (38)	2.69 (51)
6'OH-DMA	6.90 (29)	6.92 (36)	6.75 (44)

The intra-subject variability expressed interms of 90% confidence limits for %CV for $AUC_{(0-)}$ for TRT A, B and C were 4.62 - 14.35, 6.2 - 19.29 and 5.76 - 21.03 respectively. The intra-subject variability expressed interms of 90% confidence limits for %CV for Cmax for TRT A, B and C were 12.5 - 38.9, 9.16 - 28.5 and 10.35 - 37.8 respectively.

Conclusions:

1. The apparent relative oral bioavailabiltiy of the dolasetron prototype tablet to the solution, determined by comparing plasma $AUC_{(0-)}$ of the major active metabolite

(DMA) was 103.7%. The prototype tablet formulation was used in the phase III clinical efficacy studies.

2. The apparent absolute oral bioavailabiltiy of the dolasetron solution and the prtotype tablet, determined by comparing $AUC_{(0-\infty)}$ of DMA was 72.3 % and 73.6 % respectively.

3. Plasma exposure of 5'OH-DMA and 6'OH-DMA as compared to DMA after both IV and oral treatments (i.e. plasma $AUC_{(0-\infty)}$ ratios) were between for 5'OH and for 6'OH.

4. Approximately 30 and 22 % of the dose was excreted in urine as DMA after IV and oral administration of DM, respectively. The R(+) isomer accounted for the majority (>87 %) of the urinary excreted DMA regardless of the route of administration.

5. Aftre both IV and oral treatments no measurabie amount of parent drug was excreted in urine, and approximately 3 % of the dose was excreted as 5'OH-DMA and 7 % as 6'OH-DMA.