CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020624

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.

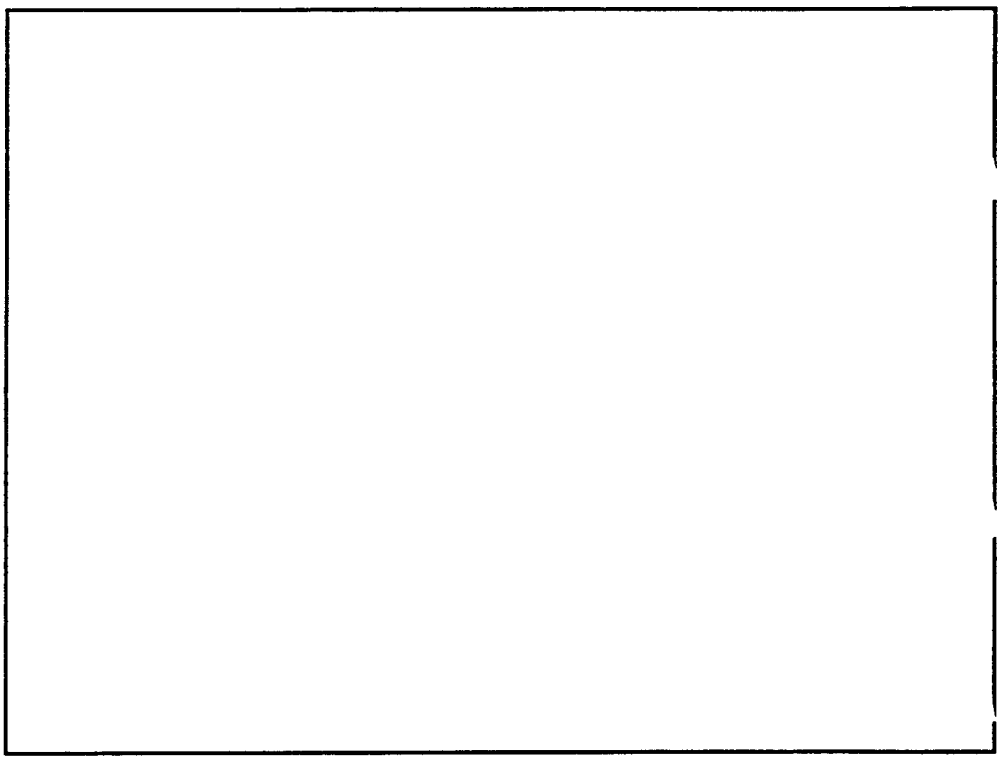
In a population PK analysis of 273 patients receiving cisplatin chemotherapy, value of DMA apparent systemic clearance (CLapp) and volume of distribution of central compartment (V) was estimated to be 0.607 L/hr/kg (%cv = 7.68) and 1.56 L/kg (%cv = 8.14), respectively. The intersubject variability in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

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

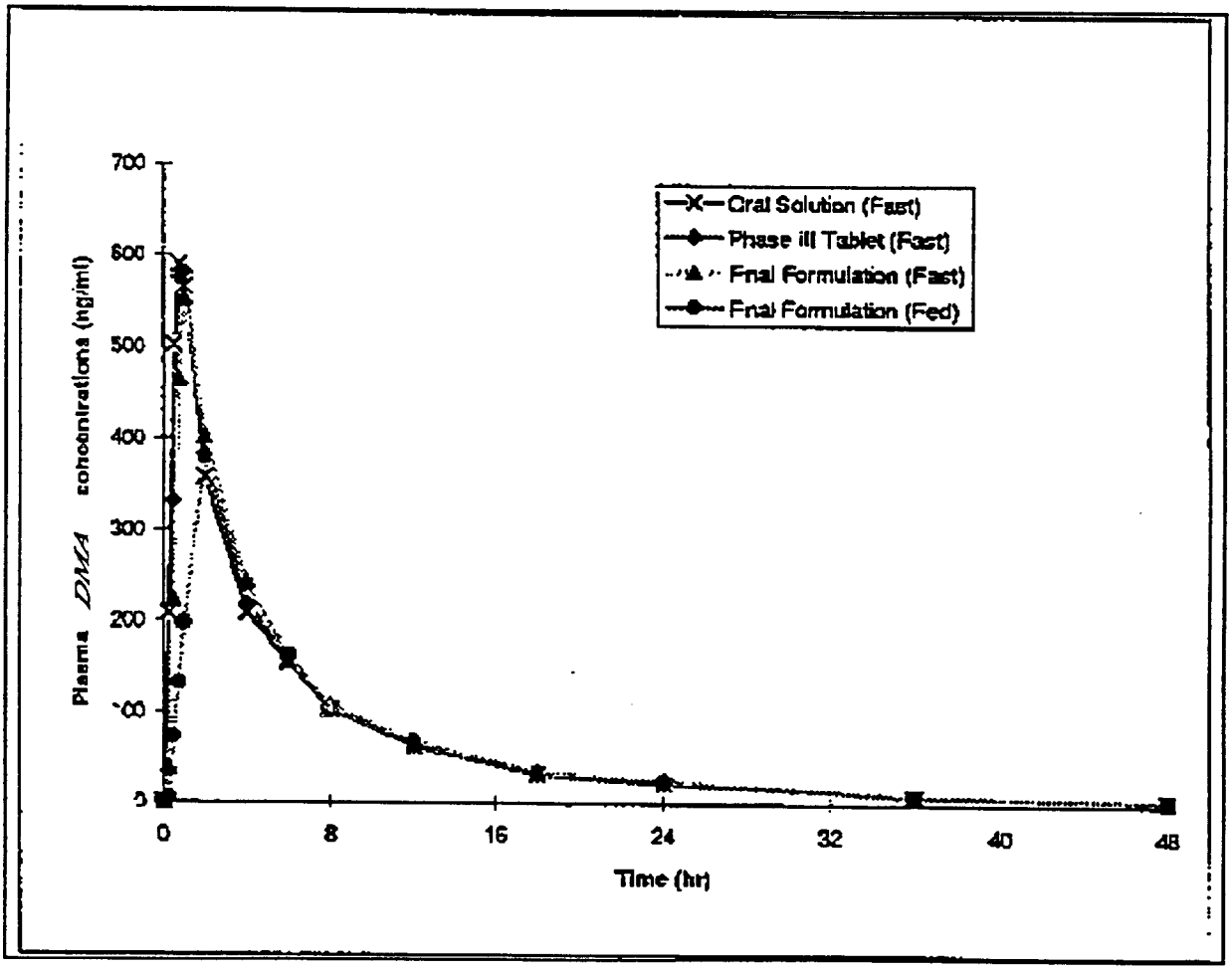
A six day drug free interval (washout period) was included between treatments. Serial plasma samples were collected for 48 hours after dosing.

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
$AUC_{(0-)}$	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
$AUC_{(0-)}$	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 $AUC_{(0-)}$ 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.

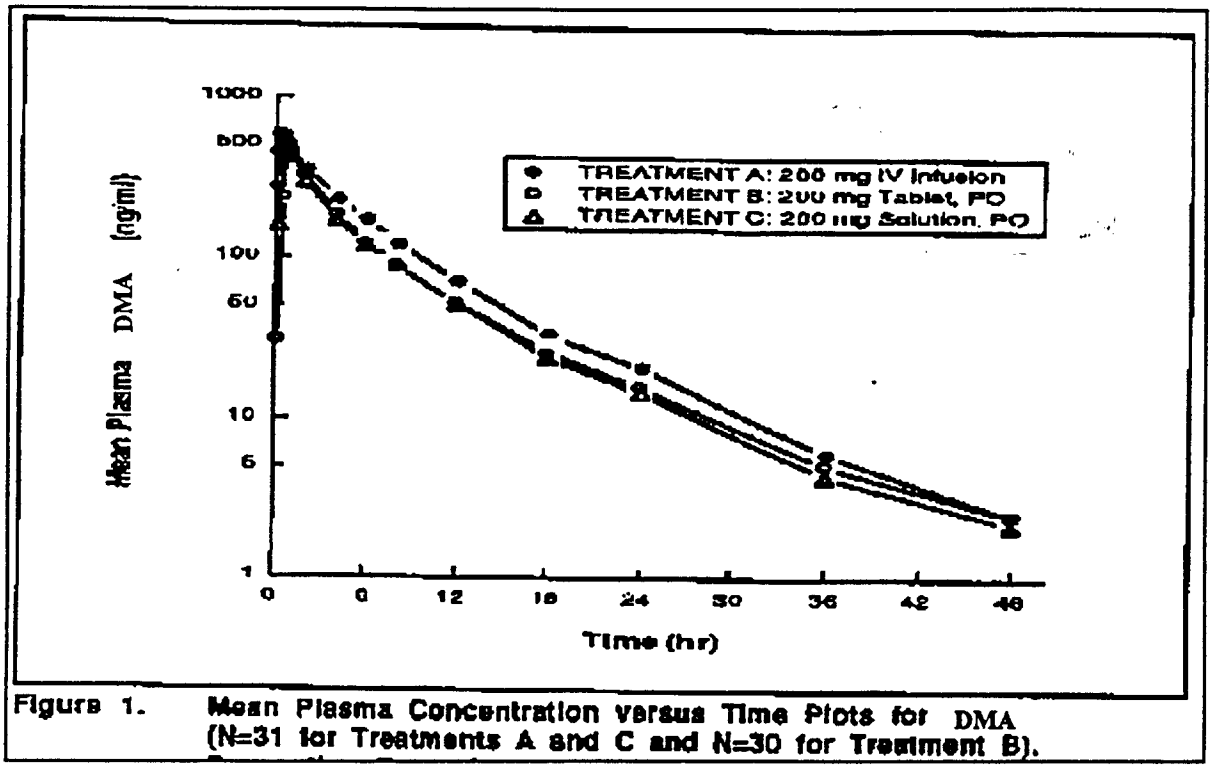


Figure 1. Mean Plasma Concentration versus Time Plots for DMA (N=31 for Treatments A and C and N=30 for Treatment B).

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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.

Dose Proportionality and Absolute Bioavailability of Dolasetron after Three IV Infusion Doses and One oral Dose in Normals

Study: MCPR0080

Objectives:

1. To determine the dose proportionality of iv administered DM,
2. To determine the absolute oral bioavailability of DM,
3. To determine pharmacokinetics of DM, total DMA and R(+) and S(-) enantiomers of DMA.
4. To investigate the effect of DM on ECG measurement after IV and oral administration.

Formulation: A 10 mg/ml injectable solution of dolasetron mesylate was used in this study for both iv and oral treatment.

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

Study Design and Sampling: The study was an open-label, randomized, complete, four-way cross-over design with 24 healthy, male subjects between the ages of years. Each subject received one of the following treatments for each period:

Treatment A: 200 mg DM given by 10 minute iv infusion.
Treatment B: 100 mg DM given by 10 minute iv infusion.
Treatment C: 50 mg DM given by 10 minute iv infusion.
Treatment D: 200 mg DM in solution given orally.

Blood samples for iv treatments (A, B and C) were collected immediately before the start of infusion, and at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 hours after the end of infusion. Blood samples for the oral treatment (D) were collected immediately before the dose, and at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 hours after the dose. Urine samples for both iv and oral treatments were collected immediately before oral dosing or the start of iv infusion, and at intervals of 0-4, 4-8, 8-12, 12-24 and 24-48 hours after oral dosing or the end of iv infusion.

Pharmacodynamic analysis was performed using NONMEM to investigate the relationship between changes in PR interval or QRS duration and plasma concentrations of the major, active metabolite of DM, DMA.

Results: Figure 1 and 2 show mean plasma concentration versus time plots for DM and total DMA, respectively. Following tables present mean pharmacokinetic parameters of DM and total DMA, respectively.

Mean PK parameters for DM

Variable	TRT	Mean	% CV
AUC_{0-} (ng*h/ml)	A	285.5	19
	B	137.6	22
	C	75.0	19
t1/2 (h)	A	0.14	15
	B	0.14	45
	C	0.14	21
CL (ml/min/kg)	A	114.9	31
	B	120.9	34
	C	110.0	33
V(L/kg)	A	1.40	27
	B	1.48	45
	C	1.35	41

Mean PK parameters for DMA

Variable	TRT	DMA (Mean, % CV)	R (+) DMA	S(-) DMA
AUC_{0-} (ng*h/ml)	A	3637.5 (33)	2801.0 (23)	764.5 (16)
	B	1796.6 (28)	1309.5 (28)	391.7 (24)
	C	909.9 (31)	645.0 (20)	209.4 (24)
	D	2680.3 (30)	2100.5 (29)	526.2 (21)
Cmax (ng/ml)	A	646.9 (29)	554.4 (29)	88.3 (21)
	B	320.4 (25)	272.5 (32)	46.4 (20)
	C	160.9 (29)	150.3 (34)	29.0 (37)
	D	601.2 (35)	522.7 (41)	105.0 (26)
tmax (h)	A	0.67 (37)	0.56 (23)	1.60 (38)

	B	0.62 (64)	0.48 (24)	1.27 (46)
	C	0.62 (61)	0.60 (31)	1.31 (51)
	D	0.74 (44)	0.71 (25)	0.48 (27)
t1/2 (h)	A	7.66 (22)	6.09 (17)	6.27 (19)
	B	7.32 (24)	5.39 (19)	5.06 (17)
	C	6.57 (33)	5.24 (18)	4.68 (15)
	D	8.84 (23)	6.96 (39)	6.89 (17)
CLapp (ml/min/kg)	A	9.48 (34)		
	B	9.39 (28)		
	C	9.31 (28)		
CLapp,po (ml/min/kg)	D	12.9 (34)		
CL_R (ml/min/kg)	A	2.91 (25)	3.46 (14)	1.52 (20)
	B	2.58 (32)	3.26 (27)	1.41 (29)
	C	2.65 (27)	3.06 (11)	1.26 (12)
	D	2.61 (28)	2.82 (26)	1.81 (21)
Vapp (l/kg)	A	6.08 (30)		
	B	5.77 (25)		
	C	5.00 (27)		
F(%)	D	76.0 (28)		

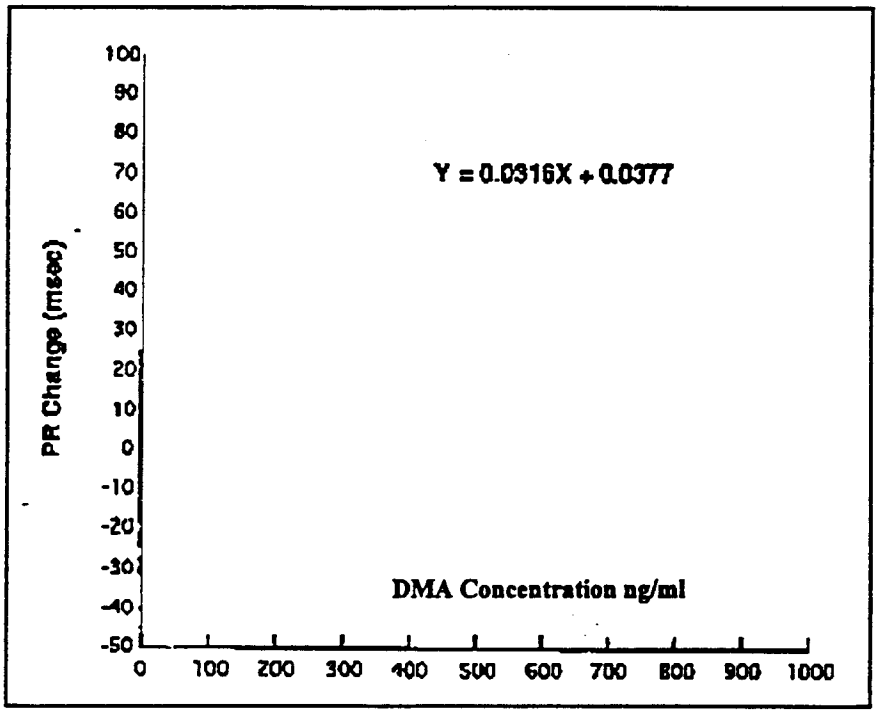
The reduction of DM to the major metabolite, DMA is a stereoselective process. The R(+) DMA represented the majority of DMA in plasma as the plasma $AUC_{0-\infty}$ and Cmax of R(+) DMA were approximately 3 to 4 times higher than those of S(-) DMA, respectively. The plasma $AUC_{0-\infty}$ of both R(+) and S(-) DMA increased proportionally with dose over the iv dose range of 50 to 200 mg DM. The increase in Cmax for R(+) DMA after administration of 50 to 200 mg DM appears to be proportional to dose, however a less proportional increase in Cmax was observed for S(-) DMA. For R(+) DMA, two fold increase in dose from 50 to 100 mg and from 100 to 200 mg resulted in 1.8 and 2.0 fold increase in Cmax, respectively. For S(-) DMA, two fold increases in dose from 50 to 100 mg and from 100 to 200 mg resulted in 1.6 and 1.9 fold increase in Cmax, respectively.

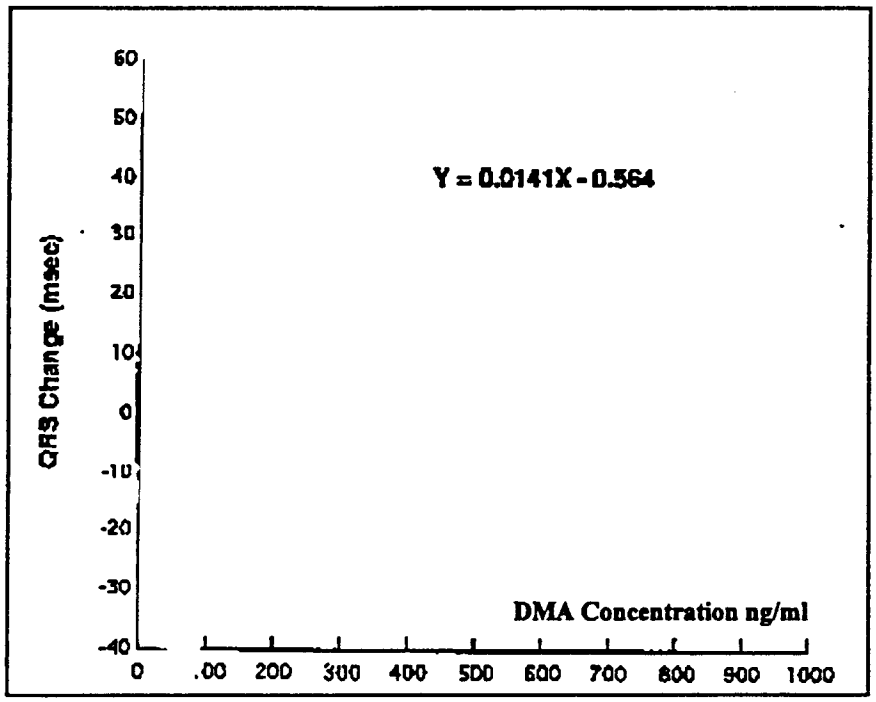
PK-PD

Approximately 30 % and 22 % of the dose were excreted in urine as DMA following iv and oral administration of DM, respectively. The majority (>86 %) of DMA was excreted in urine as R(+) DMA. Urinary excretion of total, R(+) and S(-) DMA was similar over the iv dose range

studied.

Acute and reversible changes in PR interval and QRS duration observed after 50 to 200 mg IV and 200 mg oral doses of DM were linearly related to plasma concentrations of DMA (Table 1 and 2 summarize the NONMEM model building procedure). The estimated slope for the PR change with plasma DMA concentrations for individual subjects ranged from msec/ng/ml with mean population mean of 0.0316 msec/ng/ml. Those for QRS change ranged from with a population mean of 0.0141 msec/ng/ml.The slope for both PR and QRS changes were positive in most subjects (23 out of 24), indicating PR and QRS changes increase with an increase in plasma concentration of DMA. The range of slopes for PR and QRS changes were small, indicating that small changes in PR interval and QRS duration are predicted with large changes in the plasma DMA concentration. The population predicted changes in PR interval and QRS duration over the plasma DMA concentrations observed following 50 to 200 mg IV and 200 mg oral administration of DM were less than 26 and 11 msec, respectively. The route of administration (iv and oral) had no effect on the magnitude of PR or QRS changes with plasma concentrations of DMA.





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Conclusion:

1. The plasma $AUC_{0-\infty}$ of DM increased proportionally with dose following iv administration of 50 to 200 mg DM.

2. The plasma $AUC_{0-\infty}$ and Cmax of DMA increased proportionally with dose after iv administration of 50 to 200 mg DM. The plasma $AUC_{0-\infty}$ of DMA was approximately 12 times higher than of DM.

3. The R(+) DMA accounted for the majority of DMA present in plasma (> 75 %) and urine (>86 %). The plasma $AUC_{0-\infty}$ of both R(+) and S(-) DMA increased proportionally with dose after iv administration of 50 to 200 mg DM.

4. Reversible changes in PR interval and QRS duration observed following 50 to 200 mg IV and 200 mg oral administration of DM were linearly related to plasma concentrations of DMA. The predicted increase in PR interval and QRS duration for normal subjects over the IV dose range of 50 to 200 mg DM was less than 26 msec and 11 msec, respectively.

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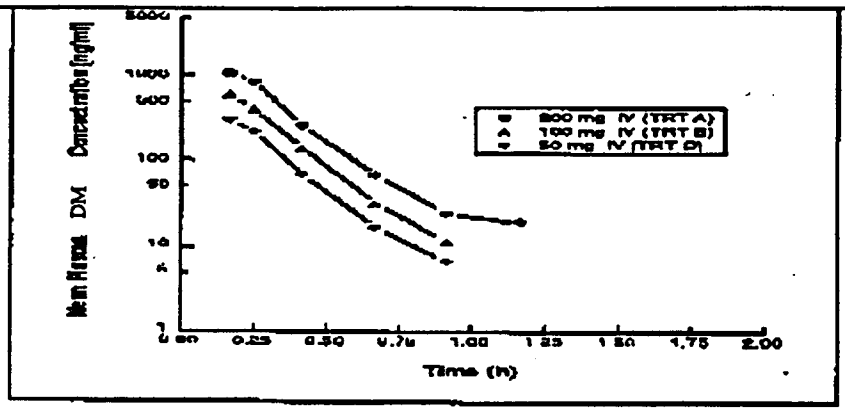


Figure 1. Mean Plasma Concentration versus Time Plots for DM (N=23)

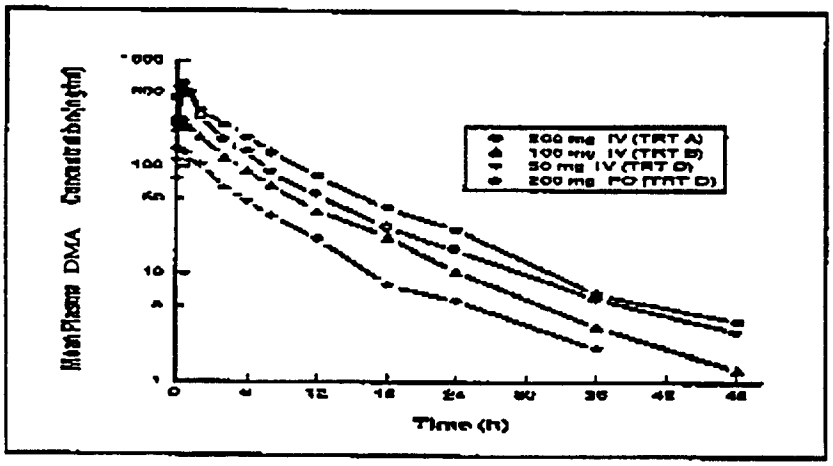


Figure 2. Mean Plasma Concentration versus Time Plots for Total DMA (N=24)

Dose Proportionality of Dolasetron after Single and Multiple Administration to Normal Volunteers

Study: MCPR0081

Objectives: To determine the dose proportionality and extent of accumulation of DM and DMA

Formulation: A 10 mg/ml injectable solution of DM was administered orally for all treatments.

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

Study Design and Sampling: The study was an open-label, randomized, three-way cross-over design with 18 healthy, male subjects between the ages of years. Each subject received one of the following treatments in each period:

Treatment A: 200 mg DM injectable solution given orally at 7:00 am on day 1 and at 7:00 am on day 3 through day 7.

Treatment B: 100 mg DM injectable solution given orally at 7:00 am on day 1 and at 7:00 am on day 3 through day 7.

Treatment C: 50 mg DM injectable solution given orally at 7:00 am on day 1 and at 7:00 am on day 3 through day 7.

Serial blood and urine samples were collected for 48 hours after the single dose on day 1 and after the last multiple dose on day 7.

Results: Figures 1 and 2 show mean plasma concentration versus time plots for DMA observed after single (day 1) and multiple (day 7) oral administration of 50 to 200 mg DM, respectively. The following tables show the mean pharmacokinetic parameters of DMA obtained after single dose and at steady state.

The parent drug DM, was not detected in urine following single and multiple oral doses of 50 to 200 mg DM. After single dose of DM, approximately , of the dose was excreted in urine as DMA. The majority (> 87 %) of DMA was excreted in urine as R(+) DMA. Approximately 2 % of the dose was excreted in urine as 5'OH-DMA, and as 6'OH-DMA. The urinary excretion of R(+) and total DMA was slightly igher after 200 mg dose than after 100 mg and 50 mg doses.

Subject #5 in this study showed very low urinary excretion of 5'OH and 6'OH DMA after both single and multiple oral doses of DM compared to other subjects in the group. Based on genotyping information, this subject was identified as a poor metabolizer (PM) for cytochrome P450 IID6 substrates. After single oral dose of DM, the plasma AUC_{0-} of DMA for this subject was about 2 times higher than the mean of other normal subjects in the group. At steady state, the plasma AUCss of DMA for this subject was within the range observed in other normal subjects in the group. The Cmax of DMA for this subject was not different from that observed in other normal subjects in the group after both single and multiple oral doses of DM. The increase in AUC_{0-} without proportional change in Cmax could be due to multiple elimination routes (i.e. renal excretion, hydroxylation, glucuronide conjugation etc.)

involved in elimination of DMA.

Table 1. Mean pharmacokinetic parameters of treatments A, B and C for DMA.

Variable	TRT	Mean	% CV
AUC_{0-} (ng.h/ml)	A	2735.1	38
	B	1181.4	39
	C	613.3	42
Cmax (ng/ml)	A	520.4	26
	B	224.6	24
	C	106.9	20
tmax (h)	A	0.81	14
	B	0.70	30
	C	0.72	24
$t_{1/2}$ (h)	A	8.86	19
	B	7.47	21
	C	7.74	36
CLapp,po (ml/min/kg)	A	13.3	36
	B	15.5	35
	C	15.2	38
CL_R (ml/min/kg)	A	2.69	31
	B	2.45	24
	C	2.16	20

Variable	TRT	Mean	% CV
AUCss (ng.h/ml)	A	3097.0	36
	B	1339.2	33
	C	672.9	42
$Cmax_{ss}$ (ng/ml)	A	579.3	34
	B	235.5	21
	C	108.1	25
$tmax_{ss}$ (h)	A	0.90	36
	B	0.91	49
	C	0.77	27
$t_{1/2}$ (h)	A	8.35	23
	B	9.00	29
	C	7.17	23
CLapp,po (ml/min/kg)	A	11.5	30
	B	13.4	34
	C	13.7	37
CL_R (ml/min/kg)	A	2.90	35
	B	2.31	22
	C	2.17	30

Conclusions:

1. DMA exhibited dose proportionality with respect to AUC and Cmax over a DM dose range of 50 to 200 mg, at single and multiple doses.
2. The accumulation index for DMA for orally administered DM (QD) over a dose range of 50 to 200 mg ranged from

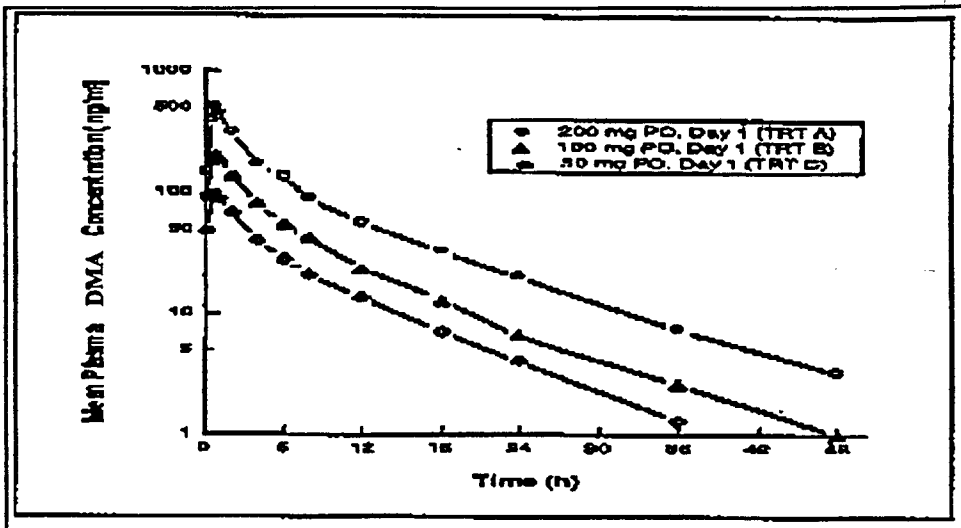


Figure 1. Mean Plasma Concentration versus Time Plots for DMA (Day 1)
(N=17 for treatments A and C, N=16 for treatment B)

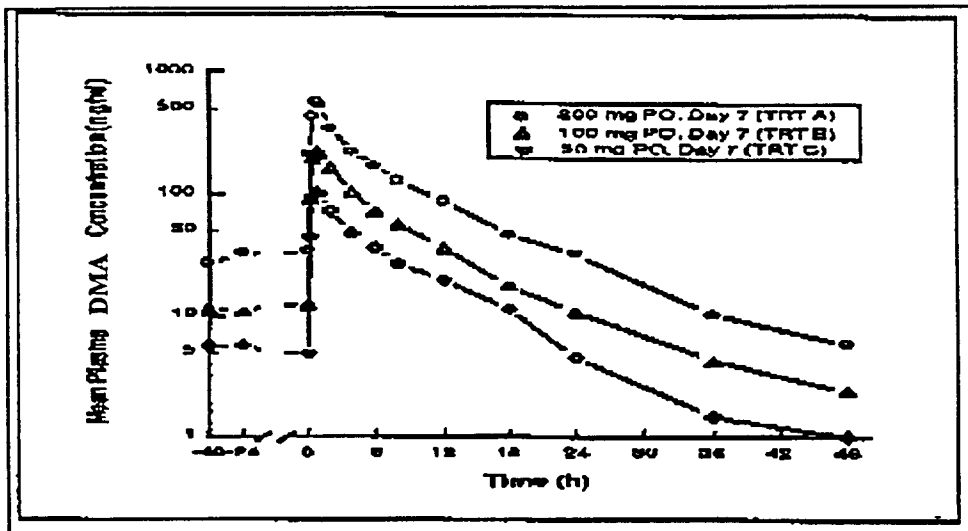
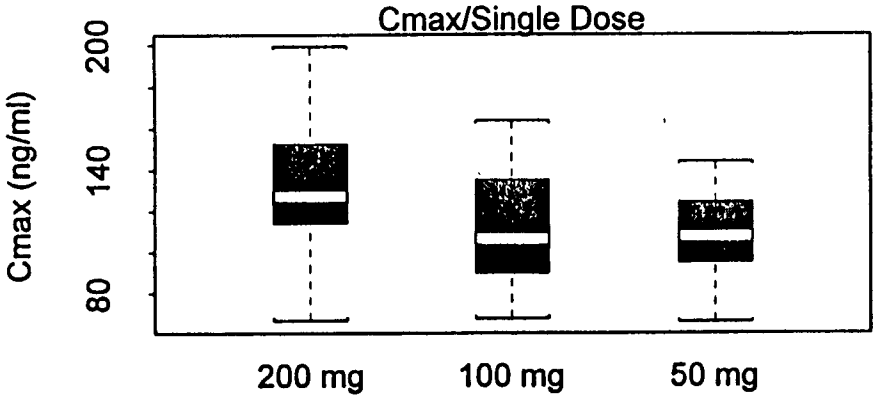
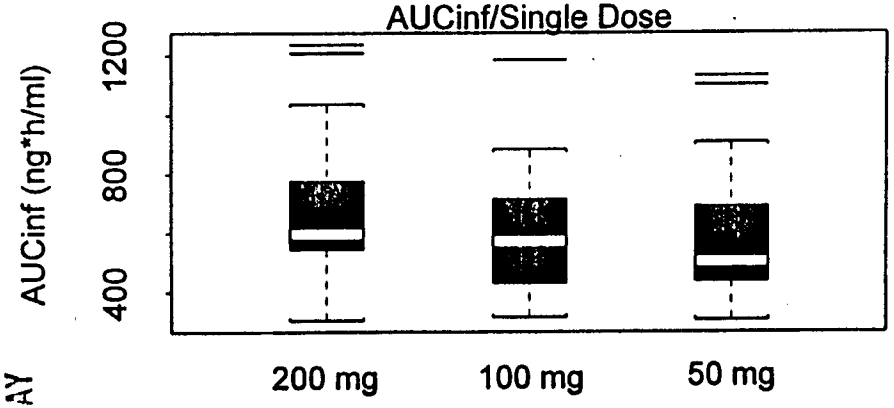
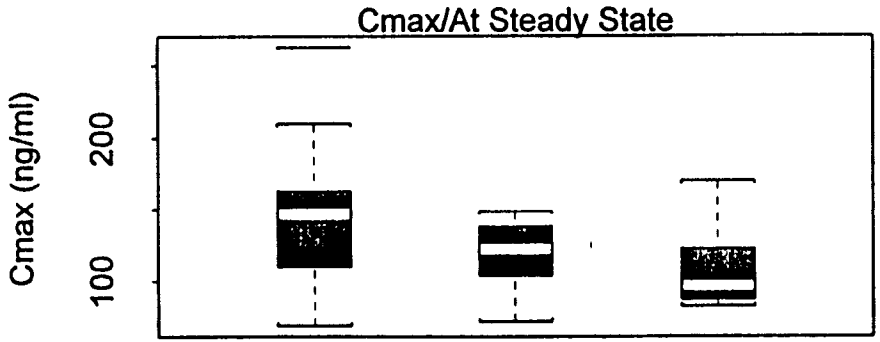


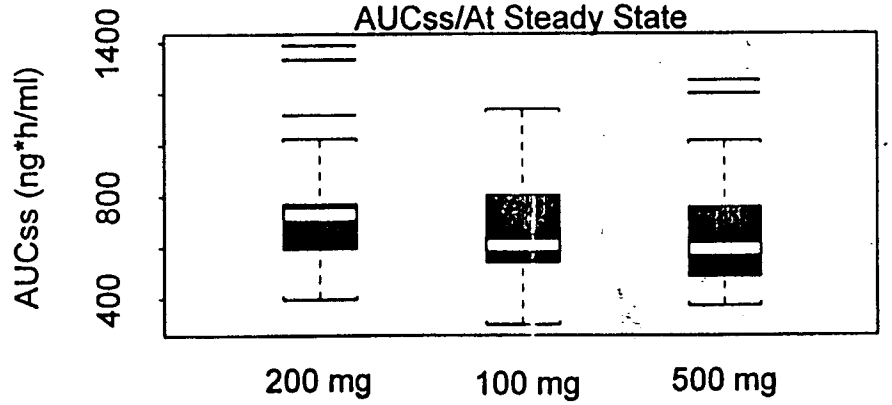
Figure 2. Mean Plasma Concentration versus Time Plots for DMA (Day 7)
(N=17 for treatments A and C, N=16 for treatment B)

Dose Proportionality/PK Parameters Normalized to 50 mg









A Randomized Double-Blind Placebo-Controlled Study of the Effects of Increasing Infusion Rates on Tolerance to and Pharmacokinetics of Intravenous Dolasetron Mesylate in Healthy Males

Study: MCPR0082

Objectives: To evaluate the safety and tolerance of healthy males to intravenous DM infused at increasing rates; assess the effects of infusion rate on the pharmacokinetics and pharmacodynamics of IV DM.

Study Design and Sampling: The study was conducted as a double blind, placebo-controlled trial in which a fixed dose of 100 mg IV DM or placebo controlled trial in which a fixed dose of 100 mg IV DM or placebo was infused into 3 parallel groups of healthy male volunteers (12 active/4 placebo for treatments A and C; 13 active /4 placebo for treatment B). The rate of infusion of DM was increased for each successive group of subjects as:

Treatment A: 100 mg dose administered over 2 minutes (50 mg/min)
Treatment B: 100 mg dose administered over 1 minutes (100 mg/min)
Treatment C: 100 mg dose administered over 0.5 minutes (200 mg/min)

Ten (10) ml of blood samples were taken just prior to and at 5 min, 15 min, 30 min, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hr after the end of infusion. Twelve-lead ECGs were obtained on study day 1 at predose and at 5 min, 15 min and 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after beginning of DM infusion.

Results: Table 1 shows the mean pharmacokinetic parameters of DM and Figure 1 shows the mean plasma DM concentration versus time plots following three treatments. Table 2 shows the mean pharmacokinetic parameters of DMA and Figure 2 shows the mean plasma DMA concentration versus time plots following three treatments.

For pharmacodynamic analysis, data form all infusion rate groups were combined since no consistent differences among the three infusion rates were observed. Figures 3 and 4 show the changes in PR and QRS intervals are linearly related to DMA concentrations observed after administration of 100 mg dose of DM in this study.

Conclusion: Pharmacokinetics of DM and DMA were not significantly altered with increase in infusion rate form 50 to 200 mg/min of dolasetron mesylate. The changes in PR and QRS intervals were best described by the changes in plasma DMA concentrations.

Table 1. Mean Pharmacokinetics of Dolasetron			
Parameter	*Treatment A*	*Treatment B*	*Treatment C*
t1/2 (min)	8.91 (5.40)@	9.91 (47.96)	9.16 (10.46)
AUC(0-∞) (ng.hr/ml)	153.13 (20.53)	190.04 (23.26)	139.79 (25.17)
CL (ml/min)	8393.23 (21.85)	6811.86 (22.74)	9413.71 (28.33)
CL (ml/min/kg)	113.71 (22.45)	95.32 (20.78)	130.04 (28.61)
Vd (L/kg)	1.47 (26.47)	1.34 (39.25)	1.75 (38.36)

@ Values in parentheses are CV, %.

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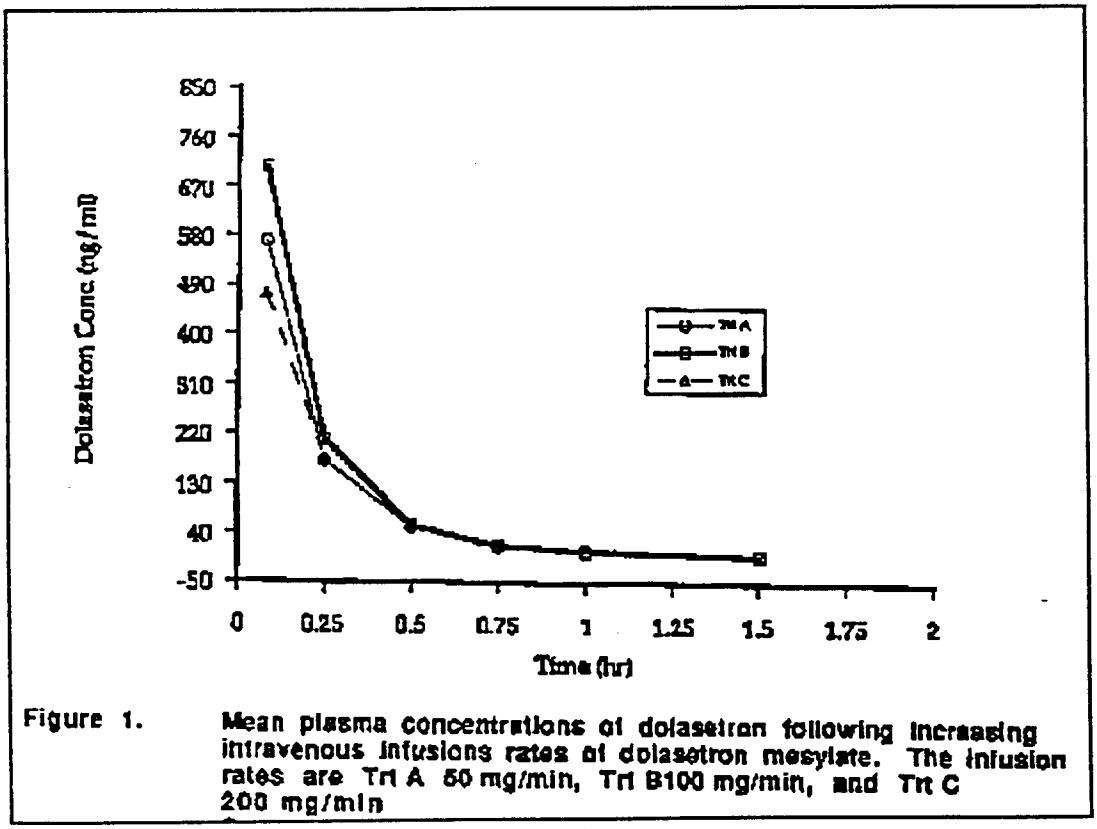

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Figure 1. Mean plasma concentrations of dolasetron following increasing intravenous infusions rates of dolasetron mesylate. The infusion rates are Trt A 50 mg/min, Trt B100 mg/min, and Trt C 200 mg/min

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Table 2. Mean Pharmacokinetics of MDL 74,156 after IV Administration of Dolasetron Mesylate

Parameter	*Treatment A*	*Treatment B*	*Treatment C*
t1/2	7.59	9.02	7.18
(hr)	(19.70)@	(21.03)	(20.54)
Cmax	279.8	313.85	290.9
(ng/ml)	(22.75)	(21.86)	(21.82)
tmax	0.40	0.52	0.50
(hr)	(32.52)	(30.84)	(42.64)
AUC(0'∞)	1679.1	1917.40	1601.2
(ng.hr/ml)	(38.04)	(46.62)	(18.97)
CLapp	823.42	733.84	806.68
(ml/min)	(30.06)	(28.73)	(23.53)
CLapp	11.15	10.20	11.13
(ml/min/kg)	(25.05)	(27.20)	(22.43)
Vdapp	7.12	7.92	7.00
(L/kg)	(21.04)	(34.74)	(40.02)

@ Values in parentheses are CV,%.

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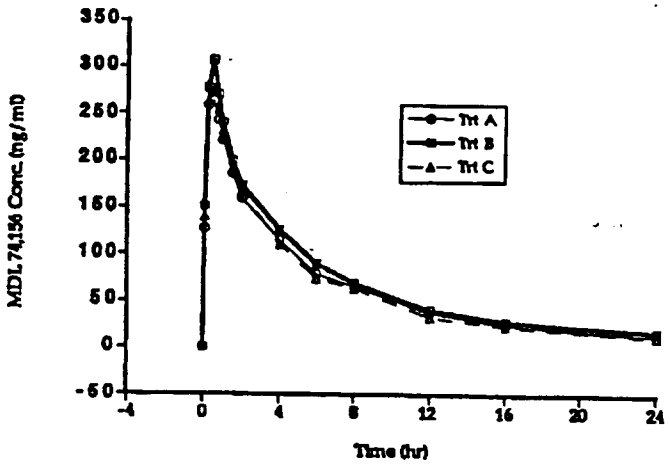


Figure 2. Mean plasma concentrations of MDL 74,156 following increasing intravenous infusion rates of dolasetron mesylate. The infusions rates are Trt A 50 mg/min, Trt B 100 mg/min, and Trt C 200 mg/min

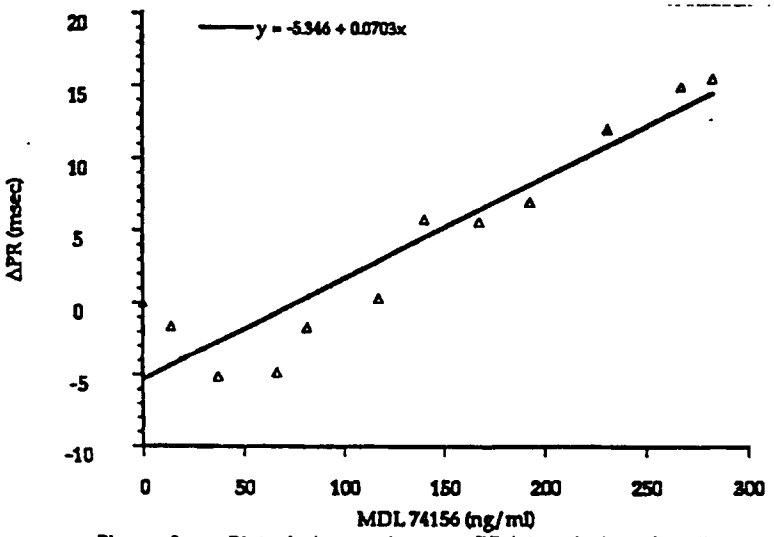


Figure 3. Plot of changes in mean PR intervals from baseline vs MDL 74,156 plasma mean concentrations. The solid line is a linear least square fit to the data.

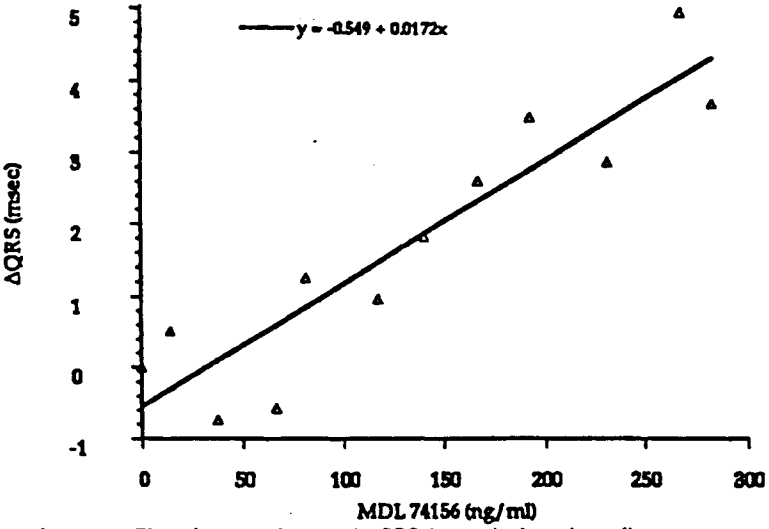


Figure 4. Plot of mean changes in QRS intervals from base line vs mean MDL 74,156 plasma concentrations. The solid line is a linear least square fit to the data.

Pharmacokinetic Evaluation of Single Oral Doses of DM for the Prevention of Acute (24 hour) Nausea and Vomiting in Pediatric Cancer Patients Receiving Moderately to Highly Emetogenic Chemotherapy

Study #: AN-PD-0292

Objectives: To evaluate the pharmacokinetics (PK) of oral DM to support the selection of the appropriate single oral dose in pediatric cancer patients.

Study Design: Doses of 0.3, 0.6, 1.2, 1.8 or 2.4 mg/kg were to be evaluated for the prevention of acute emesis in pediatric patients receiving moderately to highly emetogenic chemotherapy.

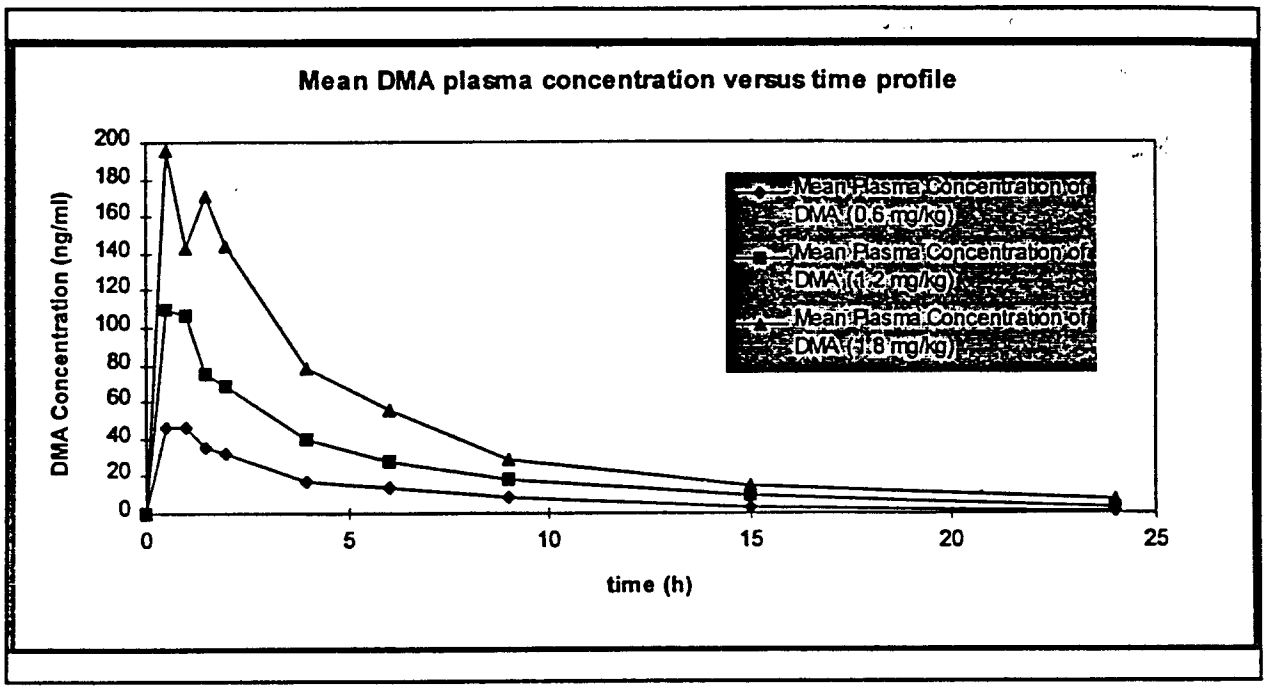
Protocol Changes: Sub-optimal efficacy results were obtained at the 0.6 mg/kg dose, so the 0.3 mg/kg dose level was not evaluated and the protocol was amended to remove this dose. Due to slow recruitment, a decision was made by the sponsor to finish the study without 2.4 mg/kg dose group as no patient had been recruited for this dose.

A total of 32 pediatric cancer patients received oral doses of 0.6 (N=9), 1.2 (N=13), or 1.8 (N=10) mg/kg of DM with apple or apple-grape juice 30 minutes prior to receiving emetogenic chemotherapy. Most of the pediatric patients (30/32) were caucasian. Serial blood samples were taken just prior to dosing, and at 0.5 (30 min), 1, 1.5, 2, 4, 6, 9, 15 and 24 hours after the end of DM oral administration.

Formulation: DM was supplied to each clinic in ampules containing 10 ml of a 20 mg/ml solution of the drug. Each dose was administered either undiluted, or diluted in a sufficient quantity of apple or apple-grape juice to make 20 ml of oral dosing solution. If the dose was administered undiluted, it was followed by apple or apple-grape juice without restriction on the quantity of juice.

Results: The mean DMA plasma concentration-time profiles for the oral doses administered in

this study are shown in the following Figure.



The following table summarizes mean (%cv) PK parameters for DMA.

Parameter	Pediatric Patients Dose (Oral)			Healthy Adult Volunteer Dose (Oral) (from study MCRP0081)		
	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 (360	7.47 (21)	8.86 (19)
$CL_{app,po}$ (ml/min/kg)	37.4 958)	40.4 (61)	32.4 (58)	15.2 (38)	15.5 (35)	13.3 (36)

The following table shows mean apparent oral clearances, half-lives and Tmax by age.

Parameter	Age Group		
	Pediatric Patients 3-11 years (N=19)	Pediatric Patients 12-17 years (N=13)	Healthy Adults 20-43 years (N=18)
$CL_{app,po}$ (ml/min/kg)	44.24 (49)	26.52 (67)	14.7 (36)
$t_{1/2}$ (h)	5.50 (39)	6.39 (30)	8.04 (27)
tmax (h)	0.93 (54)	0.97 (52)	0.75 (23)

Conclusion: For comparable doses, the mean apparent oral clearance values for the pediatric cancer patients ages 3-11 years and 12-17 years were 3 and 1.8 times greater than those observed in normal healthy adult volunteers. Maximum plasma concentration (Cmax) in pediatric cancer patients were approximately lower than those observed in healthy adults.

Pharmacokinetic Evaluation of a Single Oral Dose (1.2 mg/kg) of Dolasetron Mesylate in Children Undergoing Elective and Uncomplicated Surgery Under General Anesthesia

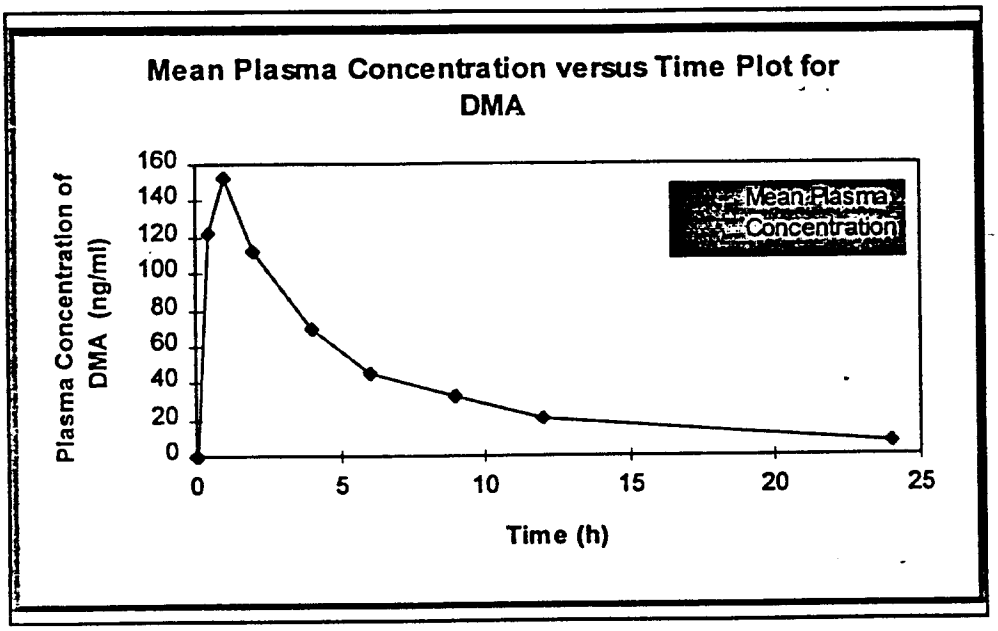
Study: AN-PD--0993

Formulation: The manufacturing history of the 20 mg/ml injectable solution (used orally) in the study is as follows:

Batch No.	92A014
Site of Manufacturing	
Date of Manufacturing	March 1992
Dosage Form	Injectable Solution
Strength	20 mg/ml
Batch Size	

Study Design and Sampling: This was an open-label, single center study. Twelve subjects (2-12 yr) received a single oral dose (1.2 mg/kg) as a solution, administered 1 to 2 hours preoperatively. Serial plasma samples were collected for 24 hours (0.5, 1, 2, 4, 6, 9, 12 and 24 hr) after dosing.

Results: The following figure presents mean plasma concentration-time plot for DMA.



The following table summarize the mean (%cv) PK parameters for DMA following oral Administration of 1.2 mg/kg DM in children undergoing general anesthesia for surgery.

Parameters	Mean (%CV)
AUC_{0-} (ng.h/ml)	933 (61)
Cmax (ng/ml)	159 (32)
tmax (h)	1.39 (70)
CLapp,po (ml/min/kg)	20.77 (49)
t1/2 (h)	5.89 (24)

Conclusions: Mean apparent clearance was 34 % greater and half-life was 21 % shorter in pediatric surgical patients than in healthy adult volunteers.

Pharmacokinetic Evaluation of Single IV Doses of DM for the Prevention of Acute (24 hour) Nausea and Vomiting in Pediatric Cancer Patients Receiving Moderately to Highly Emetogenic Chemotherapy

Study: AN-PD-0192

Objectives: To determine the appropriate single IV doses of DM for children by conducting pharmacokinetic (PK) assessments.

Formulation: DM was supplied to each clinic in ampules containing 10 ml of a 20 mg/ml

Study Design: The study was conducted as an open-label dose escalation study in pediatric patients between the ages of years old receiving moderately to highly emetogenic chemotherapy. A total of 46 pediatric cancer patients received IV infusion doses of 0.6 (n=10), 1.2 (n=12), 1.8 (n=12) or 2.4 (n=12) mg/kg of DM in Normal Saline USP. Most of (42/46) of pediatric patients were caucasian.

Serial blood samples were taken just prior to the beginning of infusion, and at 0.08 (5 min), 0.5, 1, 2, 4, 6, 9, 15 and 24 hours after the end of DM infusion.

Results: Figure 1 shows the mean DMA plasma concentrations after a single IV infusion dose of DM in pediatric cancer patients. Table 1 summarize the PK parameters of DMA. The following table shows the mean apparent clearance, half-life and Tmax by age (3 to 11 years, 12 to 17 years and adults). Apparent clearance values are highest and half-lives are lowest in the youngest age group. For the 3-11 year and the 12-17 year age groups, mean apparent oral

clearances are 2 and 1.3 times greater, respectively, compared to healthy adults.

Parameter	Age Group		
	3 - 11 yr (n = 25)	12 - 17 yr (n = 21)	Healthy Adults (n = 24)
CLapp (ml/min/kg)	19.18 (30)	12.48 (37)	9.39 (30)
t1/2 (h)	4.36 (24)	5.50 (31)	7.18 (27)
tmax (h)	0.48 (42)	0.53 (39)	0.64 (54)

Conclusion:

1. Mean apparent clearance of DMA was between : in pediatric cancer patients than in normal healthy adult subjects for the iv dose range of DM.
2. The sponsor wants to propose that no dose adjustment is necessary in pediatric group, however, no justification is provided by the sponsor.

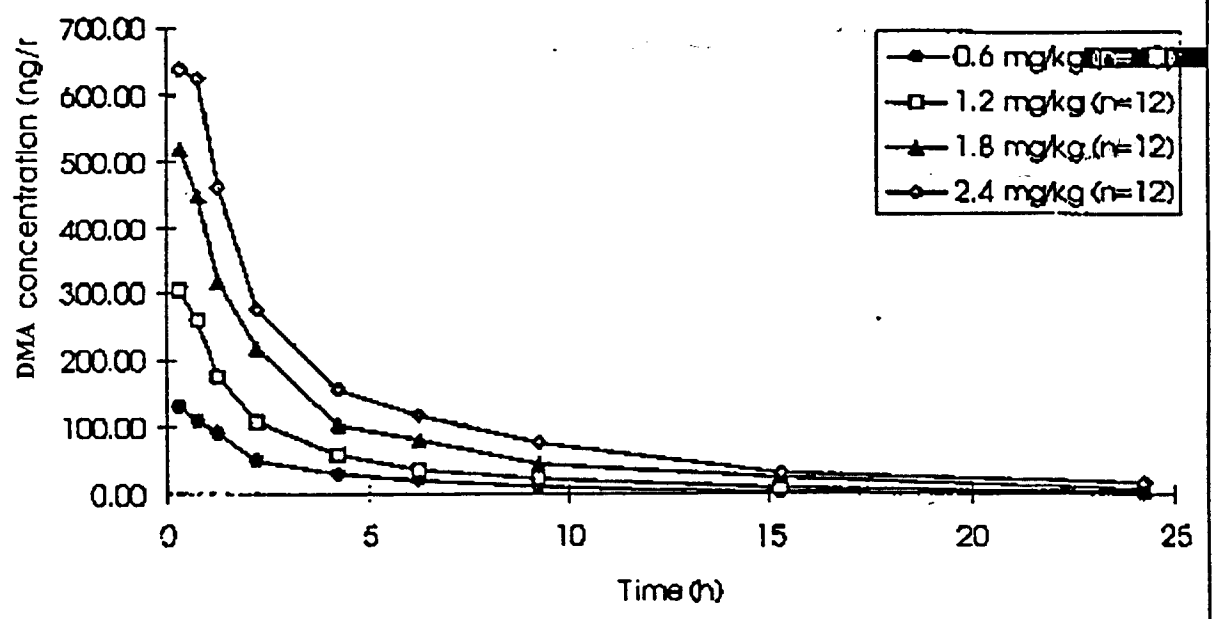


Figure 1. Mean DMA plasma concentrations after a single iv infusion dose of dolasetron mesylate in pediatric cancer patients (Source of Data: Appendix A)

Table 1. Mean* Pharmacokinetic Parameters of DMA After a Single iv Infusion Dose of Dolasetron Mesylate In Pediatric Cancer Patients and Healthy Male Volunteers

Parameter	Pediatric Patient Dose (iv)				Healthy Male Volunteer Dose (iv)** (Protocol MCPR0080)		
	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	~1.27 mg/kg N=24	~2.54 mg/kg N=24
C_{max} (ng/ml)	135.5 (24)	316.0 (34)	538.2 (45)	738.7 (53)	160.9 (28)	320.4 (25)	646.9 (29)
t_{max} (h)	0.41 (43)	0.52 (37)	0.47 (44)	0.61 (34)	0.62 (61)	0.62 (64)	0.67 (37)
AUC(0-∞) (h*ng/ml)	450.6 (37)	949.4 (36)	1881.7 (53)	2730.9 (73)	909.9 (31)	1796.5 (28)	3637.5 (33)
$t_{1/2}$ (h)	4.80 (25)	4.60 (35)	4.98 (19)	5.13 (40)	6.57 (33)	7.32 (24)	7.66 (22)
V_{app} (liters/kg)	7.43 (29)	6.80 (54)	5.89 (33)	5.91 (41)	5.00 (27)	5.77 (25)	6.08 (30)
CL_{app} (ml/min/kg)	18.83 (41)	17.17 (29)	14.29 (38)	14.65 (43)	9.31 (28)	9.39 (28)	9.48 (34)

*Percent coefficient of variation shown in parentheses
**Dose normalized by individual subject body weight (Doses 50, 100, and 200 mg, respectively
N: Number of observations

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.

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

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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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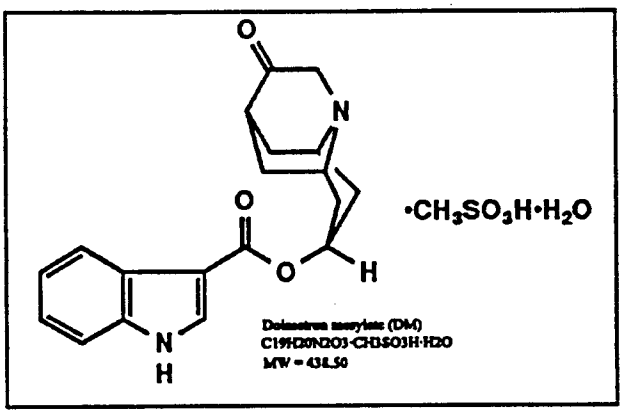
Table of Contents

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.



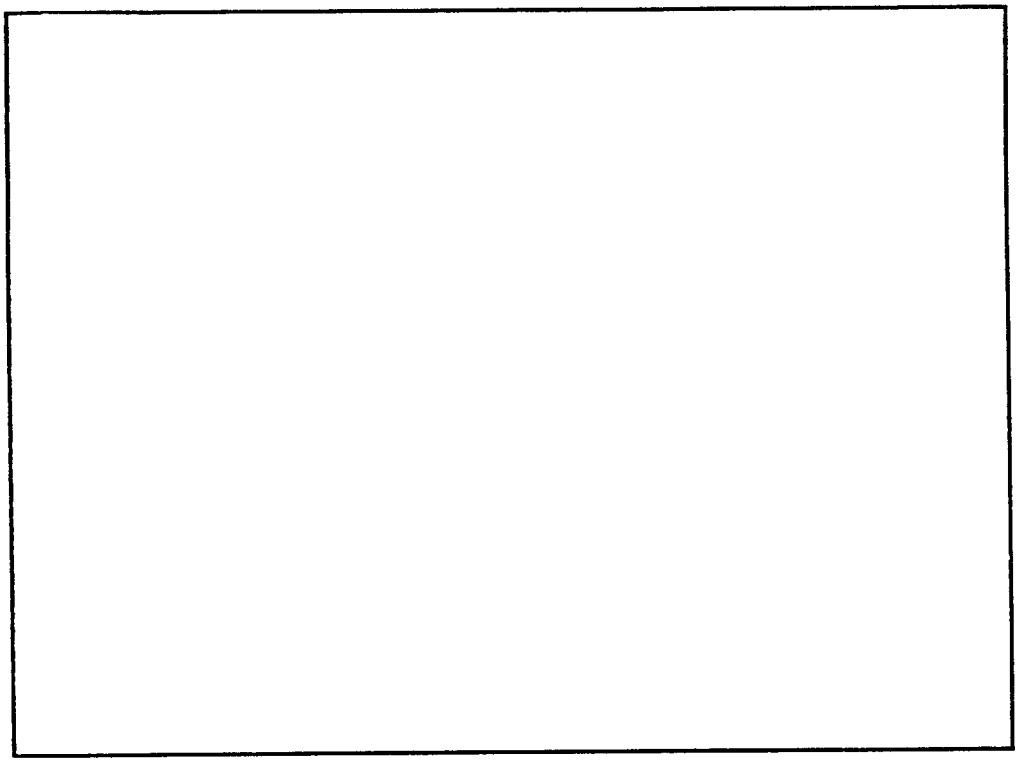
Twenty-one definitive pharmacokinetic studies have been conducted by Marion Merrell Dow Inc. to describe the human pharmacokinetics of dolasetron mesylate following oral and intravenous administration. Along with other supportive studies totalling seventeen, the data presented in this section support 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-} 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
$AUC_{0-\infty}$ (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

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)