

Table 59 Effect of Renal Insufficiency on Alosetron Pharmacokinetics

	Mean (CV Geometric LS Mean 90% CI			Geometric LS Mean Ratio 90% CI	
	Healthy Subjects Clcr ≥ 60 ml/min	Moderate Renal Failure Clcr 30 - 59 ml/min	Severe Renal Failure Clcr < 30 ml/min	Mod/Healthy Geometric Mean Ratio	Severe/Healthy Geometric Mean Ratio
AUC_∞ (ng*hr ⁻¹ /ml)	14.49 47.7 15.64 9.81-24.93	16.8 82.9 13.87 8.89-21.65	27.40 49.5 15.77 9.42-26.40	0.89 0.54-1.46 NS	1.01 0.54-1.90 NS
AUC_{0-t} (ng*hr ⁻¹ /ml)	14.21 46.7 15.36 9.63-24.53	16.65 83.3 13.7 8.77-21.42	27.16 49.8 15.57 9.29-26.10	0.89 0.54-1.47 NS	1.01 0.54-1.91 NS
C_{max} (ng/ml)	4.92 39.3 4.95 3.35-7.31	5.07 43.9 4.45 3.06-6.45	7.20 40.4 4.95 3.22-7.62	0.90 0.59-1.37 NS	1.00 0.59-1.70 NS
t_{1/2} (hours)	1.67 21.3 1.83 1.50-2.22	1.61 38.1 1.62 1.35-1.96	2.21 27.6 1.82 1.46-2.25	0.89 0.72-1.10 NS	0.99 0.76-1.3 NS
Cl/F (L/hr)	84.44 49.7 63.96 40.11-101.98	89.94 63.1 72.10 46.19-112.55	58.81 109.5 63.42 37.87-106.19	1.13 0.68-1.86 NS	0.99 0.53-1.87
V_z/F (L)	188.6 34.4 168.5 122.1-232.5	181.6 48.6 168.8 124.1-229.5	156.1 73.8 166.1 116.4-237.1	1.00 0.71-1.42 NS	0.99 0.64-1.52 NS
t_{max} (hours)	1.21 47.1 1.00	1.50 50.4 1.00	1.25 66.5 1.00	0.00 0.00-1.00 NS	0.00 -0.33-0.33 NS

Although not different statistically, the severely renally impaired subjects had higher plasma concentrations throughout the sampling period and a plot of Clcr vs. AUC appears to indicate higher AUC's in the severely impaired group.

The severely impaired group was not matched for sex, weight, or age. This group also had more women, a higher mean age, and higher mean weight. Other studies have shown higher concentrations in women and the elderly, and ANOVA indicated that there were statistically significant effects of age on C_{max}, AUC Cl/F, V/F and t_{1/2}. Although not reaching statistical significance, there was a trend for an effect of sex

on Cmax ($p = 0.057$). An interesting observation is a lower volume of distribution in the severely impaired group in spite of a larger mean total-body-weight. This could be due to difference in body composition in these subjects either due to the gender difference or wasting due to renal disease.

Several urinary metabolites were to be measured as per the protocol. However, there was no indication in the study report that they were measured. The effect of renal impairment on metabolite elimination thus cannot be determined. The urinary elimination of most metabolites without knowledge of their receptor affinities and clinical effects make an assessment of the clinical significance of their accumulation in renal insufficiency impossible.

Although alosetron is not renally eliminated to a great extent, other drugs have shown alterations in hepatic clearance in renal failure patients, presumably due to accumulation of nondialyzable substances.

6. Hepatic Insufficiency

The effect of hepatic insufficiency on alosetron pharmacokinetics was not examined. Due to the extensive metabolism and significant first pass effect hepatic insufficiency will at some point effect alosetron pharmacokinetics, and possibly alosetron pharmacodynamics.

7. Tobacco Use

The effect of tobacco use was not examined, however since alosetron is metabolized by CYP1A2 an effect on alosetron clearance is possible. Many of the pharmacokinetic studies did not exclude smokers and this could have contributed to the variability seen in alosetron pharmacokinetics. See under Effect of Inducers on Alosetron Pharmacokinetics (Page 51).

8. Diet

There are a number of dietary compounds that induce CYP1A2 and might be expected to alter alosetron and alosetron metabolite pharmacokinetics. These include tryptophan pyrolysis products found in charbroiled and fried meat and fish, indoles found in cabbage and brussel sprouts, and safoles in peppers (See APPENDIX 5). Consequently, without studying specific dietary factors the effect of diet on alosetron pharmacokinetics might be missed. For example, the design of the population pharmacokinetic study included only an assessment of the effect of a 'vegetarian diet' (See under population pharmacokinetics Page 66).

9. Achlorhydria

With a pK_a of 6.95 achlorhydria might affect alosetron absorption. (See under Effect of Inducers on Alosetron Pharmacokinetics Page 51).

L. Population Pharmacokinetics

The population model does not provide useful data beyond that already presented by the classical clinical pharmacokinetic studies. In addition, several variables that should have been explored were not. A determination of a lack of effect for certain variables cannot be established from this study. Since, effects with known effects were not identified in this analysis. Specifically the lack of an age effect and lack of differences in volume estimates in different subgroups. This is also apparent from the clearly incorrect structural model. Pharmacokinetic-pharmacodynamic relationships although not assessed would be unlikely to be established due to the poor predictability of the PK model.

Protocol S3BA2001 was a population pharmacokinetic analysis of a double-blind, placebo controlled, 12 week, dose ranging study of alosetron in subjects with irritable bowel syndrome. Subjects included male and female subjects greater than 18 years of age. Seventy subjects were to be assigned to each of five

treatment groups for a total of 350 subjects. Treatment groups included placebo, 1, 2, 4, and 8 mg alosetron po bid.

Samples were obtained at the screening, 4, 8, and 12 week visit (\pm 4 days of treatment), the date and time of last dose was collected. Factors that were assessed for their contribution to the pharmacokinetics of the drug included:

- Age
- Weight
- Height
- Sex
- Visit
- Race
- Dose
- Diet (Vegetarian/Nonvegetarian)
- Oral Contraceptive Use

According to the sponsor: 'A population pharmacokinetic analysis of sparse blood sampling data from this study showed alosetron plasma concentrations to be highly dependent on gender (40% higher in females), and slightly dependent on dose (in the 1mg-8mg range), but independent of patient age, body weight, vegetarian diet, or concomitant use of hormonal contraceptives in females.'

Subject demographics are listed in Table 60.

Table 60 Alosetron Population Pharmacokinetic Study - Subject Demographics

Variable	Male Patients (n = 66)	Female Patients (n = 149)
Age ^a	44.2 \pm 13.7 (18.6 - 93.6)	44.2 \pm 13.8 (18.3 - 73.3)
Weight ^a	86.5 \pm 16.5 (58.6 - 128.9)	75.3 \pm 20.1 (45.4 - 136.2)
Height ^a	178 \pm 7.6 (152 - 196)	165 \pm 6.7 (147 - 180)
Race ^b		
White	61	142
Other	5	7
Dose ^b		
1	14	44
2	17	33
4	16	45
8	19	27
Diet ^b		
Vegetarian	65	146
Nonvegetarian	1	3
Oral Contraceptive Use ^b		
No OC	66	109
OC	0	40

a values are mean, SD and range

b frequency

1. Sampling

From concentration vs. time graphs it appears that sampling times were adequately distributed throughout the dosage interval. Sampling times appear to range from approximately 0.5 hour post dose to 42 hours post dose. The latter time points are expected since according to the protocol, the last sample could be taken up to 4 days after the last dose.

2. Basic Structural Model

A model with first order absorption was fit to the data (ADVAN2), however estimates of k_a were consistently $> 24 \text{ hr}^{-1}$ and a model assuming instantaneous IV administration did not result in a deterioration of the fit. Thus, a one-compartment model with rapid intravenous input (ADVAN1) was deemed adequate by the sponsor.

Since this is an orally administered drug with a peak at 1 - 2 hours and since the early sampling appears to be adequate, it's obvious that the final structural model is wrong. The adequate fit of the data to a clearly erroneous structural model reflects the high degree of unexplained variability with this compound.

ADVAN2 uses separate parameters (F1, F2) to fit drug availability to the depot and central compartment respectively. The mass balance study indicates that absorption of alosetron is near 100% with a high degree of first pass, and a high degree of variability in clearance. Consequently, rather than use a structural model that fits F2 separately from clearance, the sponsor might have used a model that used the clearance to predict F_{systemic} .

Since F_{systemic} is equal to $(1 - \text{Extraction Ratio})$ and since clearance is directly related to extraction ratio by hepatic blood flow, $(Cl = Q \cdot ER)$; hepatic blood flow could have been fixed or restricted to a tighter range than F2. If we assume $F1 = 1.0$ (i.e. complete and immediate dissolution) and $Fg = 1.0$ (not intestinal metabolism).

The assumption that F1 is 1.0 is reasonable based on the mass balance data. The assumption that $Fg = 1$ is less reasonable, but must still be made since Fg cannot be determined from the presented data. Since there is an identifiability issue in fitting the data to a model containing Fg , i.e. we can't separate Fg from Fh based purely on venous plasma concentrations.

$$F1 = F_{\text{dose}}$$

$$F2 = F_{\text{systemic}}$$

$$\text{Since } F_{\text{dose}} = 1 \text{ and Dose Available} = F_{\text{dose}} \cdot \text{dose}$$

$$\text{Dose Available} = \text{Dose}$$

$$F_{\text{systemic}} = F_{\text{dose}} \cdot Fg \cdot Fh.$$

$$\text{Consequently } F_{\text{systemic}} = Fg \cdot Fh$$

$$\text{Assuming } Fg = 1.0$$

$$\text{and since } Fh = (1 - Eh) \text{ and } Clh = Qh \cdot Eh$$

Since renal clearance of unchanged alosetron is a small percentage of the total clearance (6%). It could have been ignored or fixed, and a structural model fitting Clh , with Qh fixed or adjusted with age and sex could have been employed instead of one that estimates F2 and Cl separately.

3. Predictability

The population model has poor predictability for the measured concentrations as would be expected based upon what is seen with the structural model.

4. Dose Linearity

The sponsor concluded that there was a slight nonlinearity with dose. The mean half-life was 1.3 hours with the 1 mg dose and 2.0 mg with the 8 mg dose. This 'nonlinearity' is also somewhat apparent from the concentration vs. time graphs. For the 4 mg dose approximately 10 samples were between ng/ml whereas for the 8 mg dose approximately 18 samples were between ng/ml. Although this could be a spurious finding. Earlier pharmacokinetic studies reported peak concentrations after a 1 mg dose ranged up to 25 ng/ml. Consequently, with linear kinetics an 8 fold increase in dose is expected to give concentrations up to 200 ng/ml.

5. Time Invariance

The sponsor found no indication of time invariance.

6. Age

The sponsor found no indication the age influences clearance. This is in contrast to traditional clinical pharmacology / pharmacokinetic studies.

7. Gender

Gender was found to influence clearance with males having a higher clearance. Gender was one of the most important influences found.

8. Race / Ethnicity

The sponsor found no indication that race influences clearance. This is not surprising due to the small numbers of non-white subjects (n = 12).

9. Weight / Surface Area

Clearance was not influenced by weight or obesity. Since height was available, surface area could have been calculated and clearance normalized to surface area could have been evaluated. This is often a better way to normalize.

Clearance is frequently correlated to organ size after adjusting for other factors. Since organ size is better correlated with body surface area than body weight, it's frequently better to normalize clearance to body surface area than body weight.

10. Volume of Distribution

The estimate of the mean volume of distribution for the population was 67 liters. Addition of inter-individual random error on volume did not improve the fit. Consequently, there's no indication that volume was different with different subpopulations. This is in clear contrast to earlier studies that demonstrate a difference in different subgroups.

11. Diet

There was no effect of a vegetarian diet. However, due to the small numbers of vegetarians (n = 4) no conclusions can be drawn. Since, alosetron is an indole and metabolized by CYP1A2 metabolic elimination could be induced by a variety of dietary factors. Including, flavones, methylated xanthines (caffeine), plant indoles found in cabbage and brussel sprouts, and safoles found in peppers. Tryptophan pyrolysis products formed by charcoal broiling and frying meat and fish and polyaromatic hydrocarbons found in charbroiled foods can also induce CYP1A2 (See APPENDIX 5).

12. Smoking

The influence of smoking and/or tobacco use was not examined. Due to the metabolism by CYP1A2 this should have also been examined.

13. Oral Contraceptive Use

Contraceptive use did not influence clearance.

14. Pharmacodynamics

Pharmacokinetic-pharmacodynamic (PK-PD) relationships were not assessed. However, any PK-PD relationship would be difficult to establish from this study, since the pharmacokinetic model poorly predicted measured concentrations.

V. LABELING

A. Conventions Used

The following conventions were used:

Type that is underlined like this is to be added.

Type that has a single line through it ~~like this~~ is to be deleted.

Type that is italicized *like this* needs to be discussed and examined further before specific labeling recommendations can be made

> Reviewer comments are bulleted.

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LABELING

VI. COMMENTS FOR THE SPONSOR

1. A hepatic insufficiency study should be performed. The study should enroll sufficient subjects with various types and degrees of severity of hepatobiliary disease. The various types of hepatic disease should include hepatic disease that might effect metabolism and diseases with alterations in bile acid secretion. In addition to alosetron kinetics, metabolite kinetic data should be examined.
2. Complete dissolution profiles of Lotronex™ in simulated intestinal fluid (pH 7.5) for various batches should be performed. Comparative dissolution profiles in water for the same batches should be included in the submission. Until the results of these experiments are reviewed by the FDA, it's proposed that the interim dissolution specification be
3. Additional data is needed to assess the geriatric use labeling. Constipation was dose dependent and there is an increase in alosetron exposure in the elderly. The PK/PD relationship needs to be examined and should be evaluable from currently available data.
4. Please address the following issues with regards to alosetron's metabolism.
 - a. Metabolites detected in large amounts in Japanese subjects (N-desmethyl-alosetron) were not detected in the mass balance study performed in only 2 Caucasian males.
 - b. Radiolabeled mass balance studies indicate that circulating metabolite concentrations are approximately 10 fold greater than alosetron concentrations, yet $\geq 2/3$ of the circulating radioactivity cannot be attributed to alosetron or specific identifiable metabolites based on data gleaned from various studies.
 - c. Insufficient information was provided about the contribution of metabolites to pharmacodynamic effect. e.g. 6-hydroxy-alosetron. Specifically, 6-OH alosetron is reported to be twice as potent as alosetron and is produced in large amounts presumably by the liver. It is largely eliminated in the urine, but is not detected in plasma. However, the limit of detection of 6-OH-alosetron is 6 fold greater than the Ki for 5HT₃ receptors. Circulating metabolite concentrations need to be determined in the range that might be clinically relevant. Additionally, for all metabolites, receptor affinities based upon free concentrations, protein binding, and circulating concentrations are factors that need to be considered. Information on metabolites should have included the N-desmethyl-alosetron and glucuronide conjugates since high circulating concentrations of N-desmethyl alosetron were detected in Japanese subjects and since glucuronidation of drugs does not preclude activity.
 - d. Please provide information regarding which P450 isozymes produce which metabolites, and information on which isozymes are responsible for secondary metabolism. If inhibition of individual pathways were to occur, shunting of alosetron elimination to alternative pathways would occur. Under certain conditions, this could result in an increased formation and exposure to active metabolites. Consequently, isozymes and their formation products should be identified.
 - e. Please provide multiple-dose metabolite kinetic data.
 - f. Please provide metabolite kinetic data in women.
 - g. Please provide data on the potential for metabolites to cause inhibition of drug metabolism. Free concentrations were not identified in the alosetron *in vitro* drug interaction studies and should have been considered.
5. Due to Lotronex's *in vivo* inhibition of NAT2, *in vitro* interaction studies with NAT1 should be performed.
6. Since Lotronex™ is an indole, the potential to inhibit monoamine oxidases should be examined.
7. A study to examine the effect of Lotronex™ on gastrointestinal first-pass effect of drugs with low bioavailability due to inhibition of intestinal mucosal CYP3A4 should be performed.

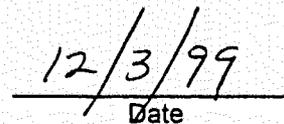
8. The effects of specific and nonspecific enzyme inducers and inhibitors on alosetron pharmacokinetics and metabolite kinetics for active metabolites should be examined.
9. There are a number of gastrointestinal symptoms associated with both Lotronex™ and with IBS. Consequently, self-medication with antacids, magnesium containing laxatives, pH altering agents, etc. are expected. Since, Lotronex™ is an imidazole with a pKa of 6.95, the effect of alterations in gastrointestinal pH on absorption and metabolite kinetics should be examined.
10. The sponsor should address the mechanism and clinical consequences of the effect of Lotronex™ on steroidogenesis.
11. For assay validations, data points should not be excluded from analysis simply due to being outliers. The intent of the validation is to obtain an estimate of the assay variability including outliers. Consequently, exclusion will give erroneous estimates of the assay variability. Inappropriate data exclusion may have occurred in assay validation (UCP/92/014).

VII. SIGNATURES



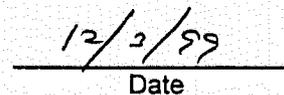
Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics


Date



FD - David Lee, Ph.D., Team Leader


Date

OCPB Briefing Meeting: Monday November 8, 1999 2:30 PM PKLN 13B45

Attendees: Ysem M, Huang S, Zhang K, Pelsor F, Mehta M, Hunt J, Chen ML,
Lee D, Lee P, Kavanagh R

CC: NDA 21-107 (orig., 1 copy)
 HFD-180 (Prizont, Senior, Gallo-Torres, Ysem, Zhang)
 HFD-181 (Levine)
 HFD-850 (Lesko, Huang)
 HFD-870 (M. Chen, Kavanagh, Lee)
 HFD-340 (Vish)
 Central Document Room (Barbara Murphy)

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APPENDIX 1 Comparative Molar Doses and Exposure of Alosetron and Other Compounds

Comparative Molar Concentrations of Alosetron and Other Compounds With Nonlinear Kinetics, Reactive Metabolites, or P450 Inhibition

Drug	Typical Single Dose (mg)	Typical Plasma Concentrations mcg/ml	Molecular Formula	MW (Base)	Dose (mM)	Approximate Plasma Concentrations		Fraction Bound (f _b)	Fraction Unbound (f _u)	Free Drug Concentration (C _f) (nM/L)	KI (nM/L)
						μM/L	nM/L				
Ethanol†		1000	C ₂ H ₆ O	46		21739	21739130				
Na Phenytoin‡	300	10-20	C ₁₅ H ₁₂ N ₂ O ₂	252	1.09	79.4	79365	0.9	0.1	7937	
Carbamazepine†	200	4-8	C ₁₅ H ₁₂ N ₂ O	236	0.85	33.9	33898	0.7-0.85	0.3	10169	
ASA†	325		C ₉ H ₈ O ₄	181	1.8			0.95			
Salicylate Anal/AP ¹		50-100	C ₇ H ₆ O ₃	138		724.6	724638		0.05	36232	
RA ²		150-300								0	
Clear Nonlinearity		715-870								0	
Theophylline†	300	10-20	C ₇ H ₈ N ₄ O ₂	180	1.67	111.1	111111	0.4	0.6	66667	
Acetaminophen*	325		C ₉ H ₈ NO ₂	151.16	2.15						
Alosetron (range)	1	0.005-0.010	C ₁₇ H ₁₈ N ₄ O	294	0.0034	0.034	3.4	0.8	0.2	0.68	
Ketoconazole	200	Mean C _{max} 3.5		531.44	0.376	6.6	6586	0.99	0.01	65.9 ³	100-700*

1 - Analgesia / Antipyresis
 2 - Rheumatoid Arthritis - possible nonlinearity
 3 - *In vitro* KI (~100 - 500 nM/L free drug)
 † - Nonlinearity Seen with Clinical Doses
 ‡ - Known Toxicity due to Reactive Metabolites
 * - total drug concentration
 ** - free drug concentration

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APPENDIX 2 Alosetron Metabolic Pathways

Indole

Imidazole

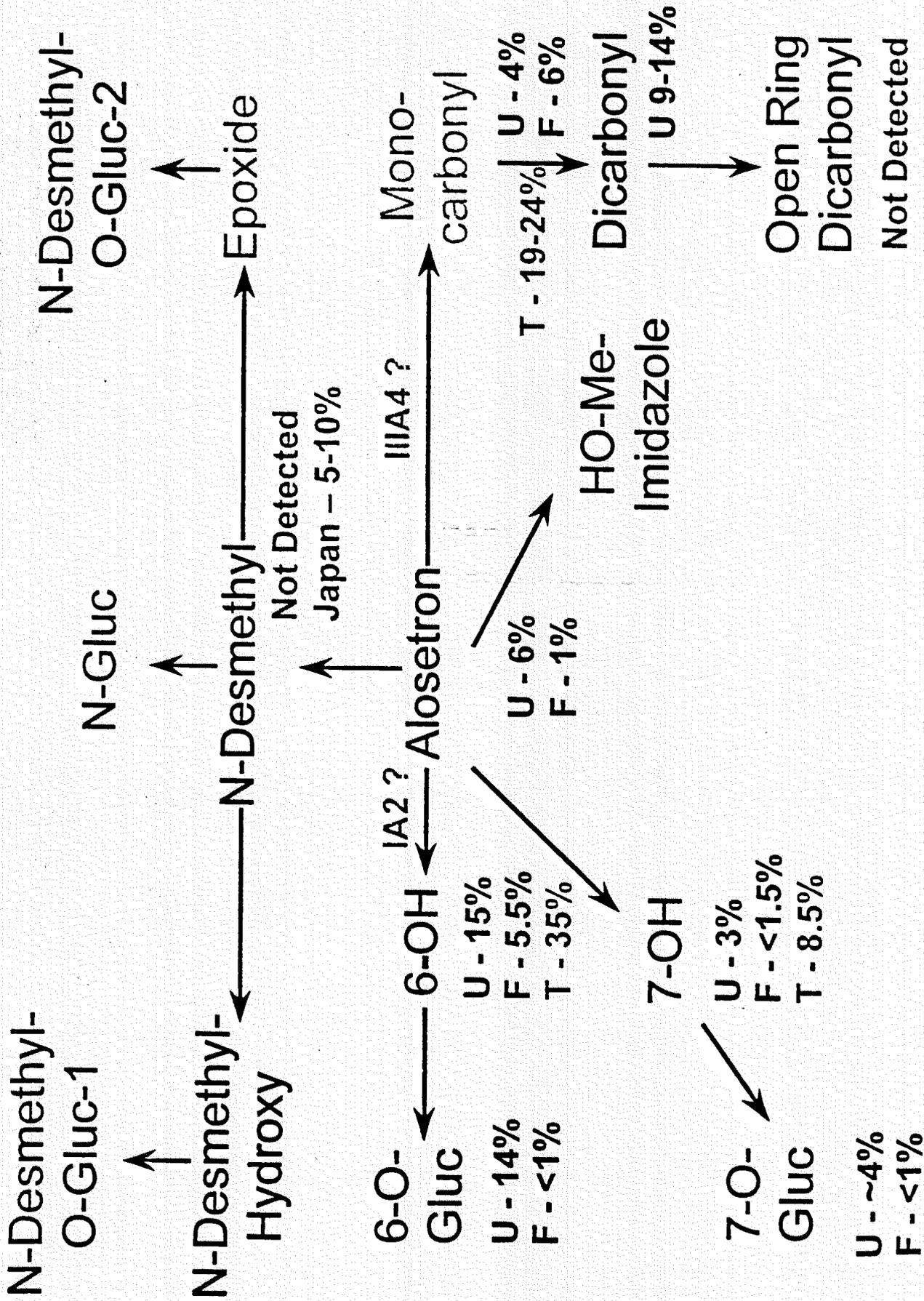
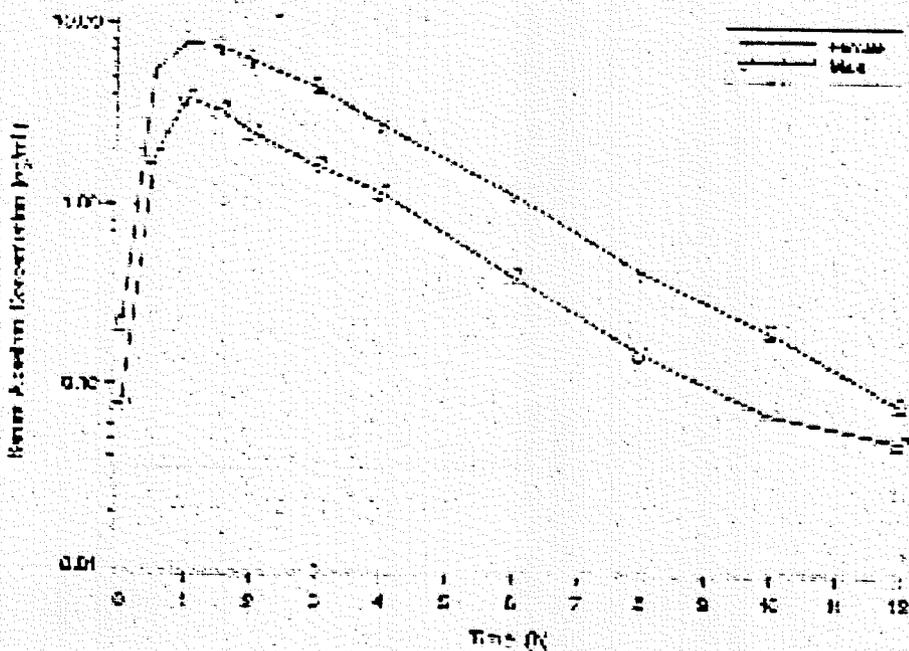
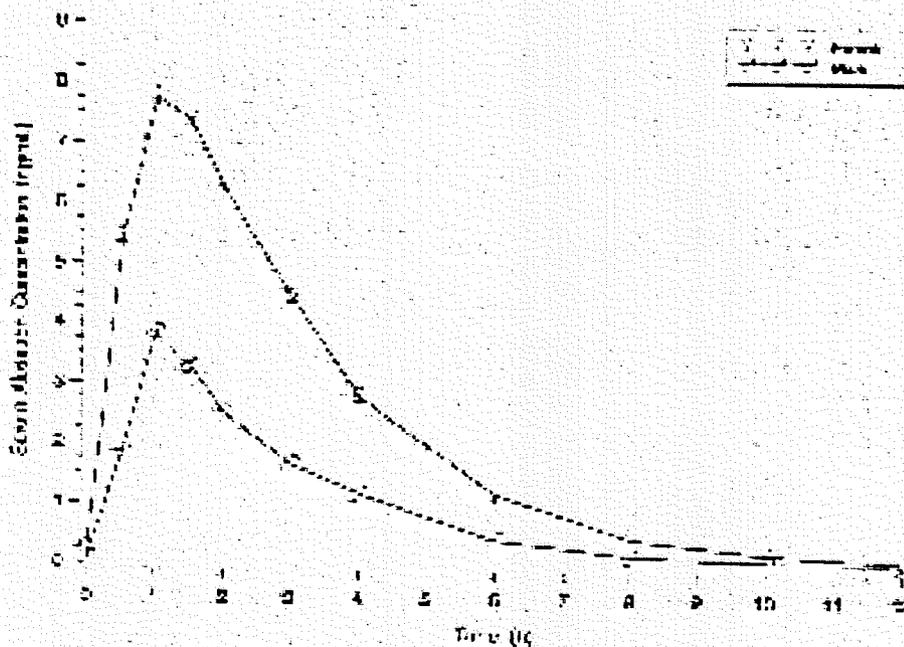


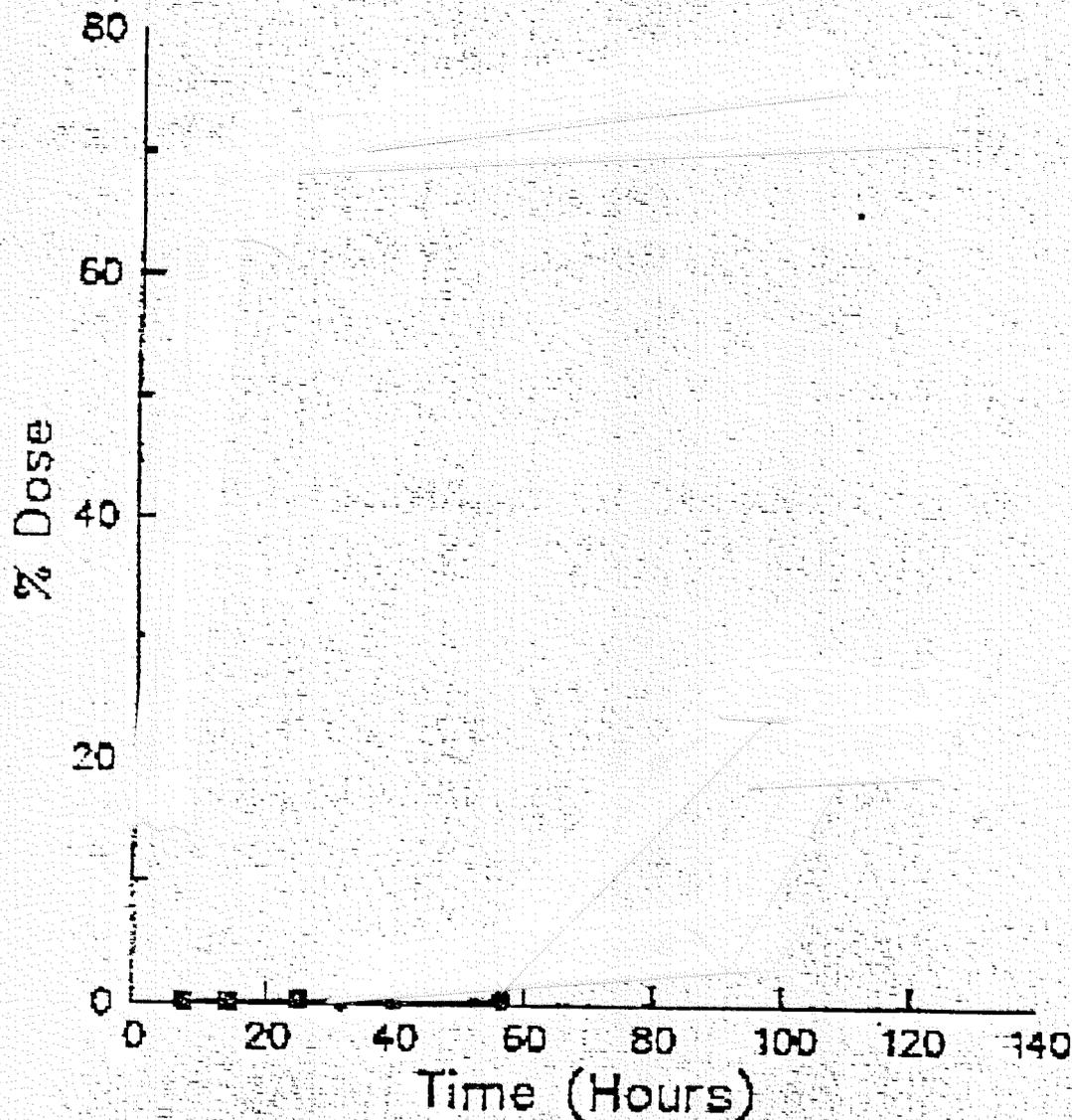
Figure of Linear and Semi-Logarithmic Plots of Median Alosetron Concentration vs. Time in Adult Females and Males following 1mg bid oral dosing of Alosetron (Day 29)

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Cumulative Excretion of Radioactive Material in the Urine and Faeces Following Single Oral Administration of ^{14}C -GR 68755 (HCl salt) to Man at a Nominal Dose Level of 4mg Base

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Volunteer 1 Urine Volunteer 2 Urine
—○— —□—
Volunteer 1 Faeces Volunteer 2 Faeces
—●— —■—