

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-107

CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)



**New Drug Application**  
**Clinical Pharmacology and Biopharmaceutics Review - Addendum 1**

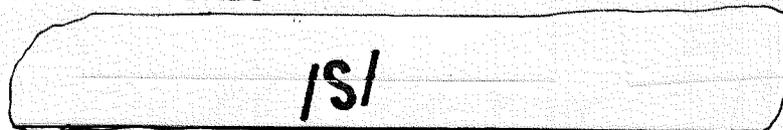
NDA:	21-107
Type of Submission:	NDA 1/P
Generic Name:	Alosetron HCl
Formulation(s);	Tablet - Immediate Release
Strength(s);	1 mg
Route(s)	PO
Brand Name:	Lotronex™
Sponsor:	Glaxo Wellcome, Inc. Research Triangle Park, NC
Submission Date(s):	June 29, 1999 August 23, 1999 September 10, 1999 September 21, 1999
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

### I. REQUESTS FOR POST-APPROVAL COMMITMENTS

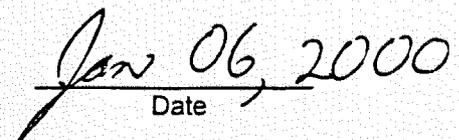
The following requests for post-approval commitments are to be sent to the sponsor. These requests are based upon discussions at the FDA internal labeling meeting held January 4, 2000.

1. The sponsor is requested to commit to perform additional studies to clarify the metabolism and disposition of alosetron in vivo. Specific issues that should be addressed include the formation of N-desmethyl-alosetron and its' metabolites, especially in Asians, and identification of the unidentified circulating metabolites from the mass balance study.
2. The sponsor is requested to commit to perform a pharmacokinetic study in subjects with hepatic impairment. In addition to alosetron kinetics, metabolite kinetic data should be examined.
3. The sponsor is requested to commit to perform additional in vitro pharmacology, drug metabolism, and drug interaction studies. These should include 5HT3 receptor affinities for any circulating or major metabolites including conjugates. Identification of P450 isozymes responsible for the formation of specific metabolites. Plus the effect of alosetron and its' metabolites on N-acetyltransferase 1 (NAT1), monoamine oxidases, and P450 isozymes as appropriate.

### II. SIGNATURES



Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

  
Date

/S/

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

1/6/2000  
Date

CC: NDA 21-107 (orig., 1 copy)  
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HFD-181 (Levine)  
HFD-850 (Lesko, Huang)  
HFD-870 (M. Chen, Kavanagh, Lee)  
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**New Drug Application**  
**Clinical Pharmacology and Biopharmaceutics Review**

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**Type of Submission:** NDA 1/P  
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**Submission Date(s):** June 29, 1999  
August 23, 1999  
September 10, 1999  
September 21, 1999  
**Reviewer:** Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

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## I. SYNOPSIS

Alosetron is a 5HT<sub>3</sub> antagonist and the proposed indication is: **'LOTROX is indicated for the treatment of irritable bowel syndrome (IBS) in female patients whose predominant bowel symptom is diarrhea,**

The proposed dosage regimen is **'1 mg taken orally twice daily with or without food'**.

The most common dose related side effect with alosetron is constipation (28%), with a mean time to onset of 3 weeks. Gastrointestinal symptoms of all types were the most commonly reported adverse events. Additionally, 2 cases of ischemic bowel disease have been observed, as well as one case of elevated hepatic transaminases associated with hyperbilirubinemia.

There is a gender difference in alosetron's efficacy with females but not males showing relief from IBS symptoms. The reason for the gender difference is unclear. However, there are several interesting observations.

Plasma concentrations in females are higher than in males, with mean peak plasma concentrations approximately 45 - 100% higher in women compared with men. Exposure to alosetron is quite variable with peak concentrations in women ranging from \_\_\_\_\_ ng/ml. Concentrations are also higher in the elderly.

Higher concentrations are due to lower total body clearance, slightly greater bioavailability, and smaller volume of distribution. These differences in clearance and volume of distribution mostly disappear upon normalization. Except in elderly females where clearance still tends to be lower even after normalization.

In males, the duration of suppression of intradermal 5-HT induced flare response (8.9 hours) is similar to the length of time alosetron concentrations obtained with a 1 mg po dose are above the *in vitro* K<sub>i</sub>. (The K<sub>i</sub> is the concentration required for 50% 5HT<sub>3</sub> receptor blockade.)

Doses higher than 1 mg po did not suppress the flare response any further in men. Higher plasma concentrations in women would be expected to result in a longer duration of 5HT<sub>3</sub> receptor blockade in women.

In clinical studies, alosetron was administered bid with food. Food decreases alosetron absorption by 25%. Consequently, with bid administration with food there may be long periods without adequate 5HT<sub>3</sub> receptor blockade in men.

Inconsistent with this hypothesis is that in dose ranging studies, doses higher than 1 mg did not show any increase in efficacy in men. However, the studies may have been underpowered to show efficacy in men. In addition, two men with the greatest response in the flare response study had the lowest alosetron concentrations. This raises the possibility that active metabolites contribute to alosetron's efficacy.

Peak metabolite concentrations are 10 times peak alosetron concentrations and total metabolite exposure is ~13 fold greater than alosetron exposure. This is due to slower elimination and a smaller volume of distribution of the metabolites. 6-hydroxy-alosetron, which is twice as potent as alosetron was not detected in plasma, although the limit of detection was ~6 fold higher than the  $K_i$  for this metabolite. 6-OH alosetron is subsequently metabolized to 6-O-alosetron glucuronide. The pattern of fecal and urinary elimination of alosetron and its' metabolites is suggestive of enterohepatic recirculation of 6-OH alosetron resulting in 'prolonged' low level exposure. Whether this would add significantly to 5HT<sub>3</sub> receptor blockade is unclear. Most of the rest of the circulating metabolites were not identified and  $K_i$ 's were not reported.

Another inconsistency that argues against the mechanism of action being mediated via 5HT<sub>3</sub> blockade the pattern of onset for efficacy. Efficacy increases rapidly over the first 2 weeks, but is not statistically different from placebo until after 4-5 weeks of treatment, after which efficacy plateaus. This is inconsistent with alosetron's half-life of 1.5 hours and mean metabolite half-life of approximately twice as long. It's possible that efficacy may be related to alosetron induced alterations in steroid hormone production. Subjects receiving alosetron demonstrate a decrease in cortisol production that becomes greater with increasing treatment duration through at least 1 month (longer periods have not been studied). Alosetron, other imidazoles including ondansetron and ketoconazole also decrease cortisol production. For ketoconazole various enzymes responsible for steroid hormone production are inhibited to different degrees and a similar scenario would not be surprising with alosetron. Consequently, there may be metabolic shunting in the production of steroid hormones or alterations in regulatory feedback with the possibility of differences between men and women.

A pharmacokinetic/pharmacodynamic study to evaluate the effect on gastrointestinal motility was performed in men. Doses used were 4 mg and plasma alosetron sampling was inadequate to characterize any pharmacokinetic/pharmacodynamic relationships. In addition, variability in motility measurements were large. Consequently, no conclusions relating alosetron use, concentrations, or clinical efficacy to effects on motility can be made.

Absorption of alosetron appears to be complete with only 1% of the dose eliminated unchanged in feces, although there is a first pass effect of approximately 50%. Since alosetron is an imidazole with a pKa of 6.95 alterations in gastrointestinal pH could alter the absorption characteristics of alosetron. This has been shown to occur with other imidazoles and should be examined further.

It should be noted that alosetron causes dose dependent constipation and the use of laxatives is recommended in the labeling, even though their use was excluded in clinical trials. This is noteworthy since patients might self medicate with magnesium containing laxatives, e.g. milk of magnesia, or with antacids for symptoms of IBS; and both classes of drugs increase gastrointestinal pH and might decrease alosetron absorption.

Because of the dose related constipation and the approximately 50% higher concentrations in elderly women compared to young women a subgroup analysis needs to be performed. This should include an analysis of efficacy and side effects in different age groups. In general, the elderly have a higher incidence of constipation even without drugs. If there is a higher incidence of dose related constipation in the elderly, a lower efficacy in younger women, or both due to differences in pharmacokinetics, the risk benefit profile of this agent would change depending upon the patient subgroup.

*In vitro* alosetron is metabolized by CYP 1A2, 2C9 and 3A4. There is also significant metabolism by non-P450 metabolic pathways (11%). *In vivo* approximately 35% of the dose is metabolized to 6-OH-alosetron and 8.5% to 7-OH-alosetron, both of which undergo secondary glucuronidation. 20-25% of the dose is metabolized to a bisoxo compound, which is likely a monocarbonyl. There is also evidence for an

epoxide intermediate. Conflicting results are reported for N-desmethylation, with up to 30% of dose eliminated as N-desmethyl-alosetron in Japanese subjects, with none detected in 2 Caucasian males in the mass balance study. In total 13 metabolite peaks have been detected in human urine, although not all have been identified.

The non-P450 pathway accounting for 11% of the elimination *in vitro* was not examined further. However, considering that indoles are metabolized by monoamine oxidase, this pathway and its products should be examined, as well as the potential for alosetron to inhibit monoamine oxidase.

Hepatic insufficiency studies have not been performed.

Approximately, 6-7% of the dose is eliminated unchanged in the urine. However, there was a near doubling of mean AUC in subjects with creatinine clearances of < 30 ml/min. This might have been due to an imbalance in the study population, but there were too few subjects to confirm this. In addition, there was no examination if there is accumulation of active metabolites, and an assessment of the effect of end-stage renal disease on hepatic metabolism was not examined. Thus, no conclusions can be drawn regarding dosage adjustment in renal insufficiency. An additional study is thus needed to clarify if dosage adjustment is needed in renal insufficiency.

Ethnic group differences have not been adequately studied, although the consistent detection of N-desmethyl-alosetron in Japanese with none detected in Caucasians has not been explained. This might have clinical consequences, since the N-desmethyl metabolite is secondarily metabolized to an epoxide in lower animals.

Drug interaction studies are both conflicting and incomplete.

Information on the potential for alosetron to cause metabolic inhibition is incomplete. *In vitro* results of experiments examining the inhibition by alosetron for P450 isozymes are internally inconsistent. However, inhibition is most likely to occur with 1A2 and 2E1, and possibly with 3A4. The molar concentrations used, i.e. 200 and 2000 nM/L, are equivalent to alosetron concentrations of 165.4 and 1654 ng/ml respectively. Peak concentrations observed with a 1 mg dose were as high as 75 nM/L. Thus, plasma concentrations are in a range where P450 inhibition may be observed inconsistently *in vivo* with clinical doses. This data suggests that alosetron is an extremely potent enzyme inhibitor and the lack of consistently observed inhibition *in vivo* may be due to low concentrations relative to  $K_i$  *in vivo* and the variability in exposure between subjects.

Due to localization of CYP3A4 on the intestinal microvilli and higher alosetron concentrations in the intestines compared with plasma, oral bioavailability of some drugs with high intestinal first pass, such as cyclosporine or midazolam might increase significantly. Although there is the possibility of off label use of cisapride, which is metabolized by CYP3A4, to treat severe constipation, an interaction study showed no effect of alosetron on cisapride pharmacokinetics. However, interaction studies examining alosetron's effect on the bioavailability of certain orally administered drugs is still warranted.

In metabolic probe studies, alosetron inhibited CYP1A2 metabolism of caffeine and NAT2 metabolism of dapsone. Formal *in vivo* drug interaction studies did not show inhibition of CYP1A2 metabolism of theophylline or CYP3A4 metabolism of other drugs. Based upon the data this reviewer does not believe there is a clinically significant inhibition of CYP1A2. The probe study was conducted after dosing for *In vivo* studies were not conducted on the effect on acetylation. Since, NAT2 is polymorphic and slow acetylation status has been shown to be clinically significant, inhibition of acetylation by alosetron should be examined further. Inhibition of NAT1 was not examined either *in vitro* or *in vivo* and should be assessed *in vitro*.

There is no information on the ability of alosetron to induce the metabolism of other drugs. Induction frequently occurs with continued dosing with drugs that initially cause inhibition.

The effect of enzyme inhibitors on alosetron pharmacokinetics has not been studied. Since alosetron

exhibits linear kinetics and the molar concentrations are so low, nonlinear kinetics should not occur, unless a metabolite that's a potent inhibitor is produced. Consequently, the only potential clinical issue would be the effect of shunting to various metabolic pathways.

The effect of enzyme inducers on alosetron pharmacokinetics has not been examined. Inducers could either decrease efficacy by decreasing alosetron exposure or increase efficacy and/or toxicity by increasing exposure to metabolites.

Potent inducers of CYP1A2 include dietary and environmental factors such as safoles in peppers, polyaromatic hydrocarbons in charbroiled meats and tobacco smoke, tryptophan pyrolysis products in charcoal broiled and fried meats and fish, and indoles in cabbage and brussel sprouts. Induction of elimination needs to be examined further.

The role of metabolites and their receptor binding, pharmacokinetics and *in vitro* potential to cause drug interactions have not been adequately examined and needs further investigation.

No bioequivalence studies with the to-be-marketed commercial scale batches have been performed. However, the to-be-marketed formulations are not qualitatively or quantitatively different from the development batches, and the pharmacokinetics for 4 mg development tablets and a 4 mg oral solution are similar and are dose proportional to the 1 mg tablets. Formulation effects are thus unlikely.

Due to the minimal difference in the to-be-marketed formulation compared with the clinical trial formulation. The bioequivalence requirement comparing Lotronex™ prepared in a 'commercial' batch to Lotronex™ clinical trial batches is waived.

Tablet dissolution of alosetron is rapid with near complete dissolution by \_\_\_\_\_ Consequently, the sponsor has proposed a release specification, Q of \_\_\_\_\_ During development increased compression pressure resulted in an increase in tablet hardness and \_\_\_\_\_ dissolution at \_\_\_\_\_ Dissolution data from recent commercial scale batches show a \_\_\_\_\_ in the percent dissolved at \_\_\_\_\_ compared to earlier batches and especially compared to clinical trial batches. The implications of this are unclear. Currently, proposed release specifications \_\_\_\_\_ are just as likely to be obtained at \_\_\_\_\_, yet would be more discriminating. Solutions other than water may be more discriminating. Additional information may be needed so that appropriate dissolution specifications can be set.

## II. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA # 21-107 submitted June 29, 1999. The overall Human Pharmacokinetic Section requires additional studies. These studies would be acceptable as a phase IV commitment. Dissolution specifications need to be determined. This recommendation and the comments for the sponsor should be sent to the sponsor. Labeling counterproposals, and selected labeling comments, should be sent to the sponsor as appropriate.

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## Table of Contents

I. SYNOPSIS.....	1
II. RECOMMENDATION.....	4
TABLE OF CONTENTS.....	5
LIST OF TABLES.....	6
LIST OF APPENDICES.....	8
LIST OF ABBREVIATIONS.....	8
III. CHEMISTRY.....	10
A. STRUCTURE.....	10
B. MOLECULAR FORMULA.....	10
C. MOLECULAR WEIGHT.....	10
D. ISOMERISM AND STEREOISOMERISM.....	10
E. PKA, PARTITION COEFFICIENT (LOG P), AND PH.....	10
F. SOLID STATE FORMS.....	10
G. SOLUBILITY.....	11
H. TABLET FORMULATIONS.....	11
1. Composition.....	11
2. Formulations Used in Pharmacokinetic Studies.....	12
I. DISSOLUTION.....	14
J. BIOANALYTIC ASSAY VALIDATION.....	16
1. Alosetron Assays.....	16
2. Assays of Other Compounds.....	17
IV. PHARMACOKINETICS / PHARMACODYNAMICS.....	18
A. LINEARITY WITH DOSE.....	18
1. Oral Administration.....	18
2. Intravenous Administration.....	20
B. MULTIPLE DOSE PHARMACOKINETICS - TIME INVARIANCE.....	21
C. ABSORPTION AND BIOAVAILABILITY.....	24
1. Bioavailability - Drug Substance.....	24
2. Bioavailability - Drug Product.....	26
3. Food Effect.....	28
D. BIOEQUIVALENCE - WITH THE TO-BE-MARKETED FORMULATION.....	29
E. DRUG METABOLISM.....	29
1. In Vitro Oxidative Metabolism of Alosetron.....	29
2. In Vivo Metabolism and Mass Balance of Alosetron.....	30
3. Metabolite Kinetics.....	33
F. RENAL ELIMINATION.....	35
G. PROTEIN BINDING.....	35
H. RBC PARTITIONING (WBP/91/047).....	35
I. ALOSETRON PHARMACOKINETICS - PHARMACODYNAMICS.....	35
1. Pharmacokinetic - Pharmacodynamic Correlations.....	35
a) 5-HT <sub>2</sub> Receptor Blockade.....	35
(1) Flare Response - IV Alosetron (Study GHP-90:16).....	35
(2) Flare Response - PO Alosetron (Study GHP-90:27).....	37
(3) PD - Colonic Motility (Study SB331007).....	38
2. 5-HT <sub>2</sub> Receptor Affinities for Alosetron and Metabolites.....	38
3. Metabolite Plasma Concentrations.....	39
a) N-Desmethyl-Alosetron (GR87620).....	39
b) Hydroxymethyl-Alosetron (GR169307).....	40
c) 6-OH and 7-OH-Alosetron.....	40
d) bis-Oxidized Alosetron (Dicarbonyl).....	41

J.	DRUG INTERACTIONS .....	43
1.	<i>In Vitro Inhibition by Alosetron</i> .....	43
2.	<i>In Vivo Inhibition by Alosetron</i> .....	44
a)	Metabolic Probes.....	44
b)	Theophylline (IA2).....	45
c)	Min Ovril .....	47
d)	Haloperidol.....	47
e)	Cisapride (CYP11A4).....	48
f)	Cortisol Production.....	49
3.	<i>Effect of Inhibitors on Alosetron Pharmacokinetics</i> .....	51
4.	<i>Effect of Inducers on Alosetron Pharmacokinetics</i> .....	51
5.	<i>Other Mechanisms</i> .....	52
K.	SPECIAL POPULATIONS.....	52
1.	<i>Special Population - Elderly</i> .....	52
2.	<i>Special Population - Pediatrics</i> .....	56
3.	<i>Gender Effects</i> .....	56
4.	<i>Race &amp; Ethnicity</i> .....	60
5.	<i>Renal Insufficiency</i> .....	60
6.	<i>Hepatic Insufficiency</i> .....	63
7.	<i>Tobacco Use</i> .....	63
8.	<i>Diet</i> .....	63
9.	<i>Achlorhydria</i> .....	63
L.	POPULATION PHARMACOKINETICS.....	63
1.	<i>Sampling</i> .....	64
2.	<i>Basic Structural Model</i> .....	65
3.	<i>Predictability</i> .....	65
4.	<i>Dose Linearity</i> .....	65
5.	<i>Time Invariance</i> .....	66
6.	<i>Age</i> .....	66
7.	<i>Gender</i> .....	66
8.	<i>Race / Ethnicity</i> .....	66
9.	<i>Weight / Surface Area</i> .....	66
10.	<i>Volume of Distribution</i> .....	66
11.	<i>Diet</i> .....	66
12.	<i>Smoking</i> .....	66
13.	<i>Oral Contraceptive Use</i> .....	66
14.	<i>Pharmacodynamics</i> .....	67
V.	LABELING.....	67
A.	CONVENTIONS USED.....	67
B.	PACKAGE INSERT.....	68
VI.	COMMENTS FOR THE SPONSOR.....	81
VII.	SIGNATURES.....	82

**List of Tables**

Table 1	Solubility of Alosetron HCl at 21 °C	11
Table 2	Composition of Tablet Formulations used in Pharmacokinetic Studies	11
Table 3	Composition of Tablet Formulations used in Phase II Dose Ranging Studies	12
Table 4	List of Pharmacokinetic Studies and Formulations Used	12
Table 5	Proposed Dissolution Method and Specification for Lotronex® (alosectron) 1 mg Tablets	14
Table 6	Alosetron 1 mg Tablet Dissolution Data	14

Table 7	Alosetron Assays	16
Table 8	Assays for Drugs Used for <i>In Vivo</i> Drug Interaction Studies	17
Table 9	Pharmacokinetic Metrics After a Single Rising Oral Dose of Alosetron Solution in Grapefruit Juice	19
Table 10	Dose Normalized Pharmacokinetic Metrics after the First Dose - Protocol S3B-101	19
Table 11	Pharmacokinetic Metrics After a Single Rising Oral Dose in Japanese Males	20
Table 12	Pharmacokinetic Metrics After a 4 mg IV Dose - Protocol GHP:89:23	20
Table 13	Dose Linearity with Intravenous Administration	21
Table 14	Multiple Dose Pharmacokinetic Metrics - 3.5 days	22
Table 15	Multiple Dose Pharmacokinetic Metrics in Japanese Males - 6.5 days	22
Table 16	Multiple Dose Pharmacokinetic Metrics - 9.5 days - Protocol GPK:90:02	23
Table 17	Alosetron 1 mg po Multiple Dose Pharmacokinetic Metrics in Males and Females over 29 days - Protocol S3BB1011	23
Table 18	Alosetron 1mg po Multiple Dose Pharmacokinetic Metrics in Males - 29 days	24
Table 19	Absolute Bioavailability of Alosetron Drug Substance - Study GHP:89:44	25
Table 20	Alosetron Solution - Additional Oral Pharmacokinetic Metrics	25
Table 21	Absolute Bioavailability of Alosetron Drug Substance and Drug Product - Protocol GHP:90:13	26
Table 22	Relative Bioavailability of Alosetron Tablets and Solution - Protocol GHP:90:13	26
Table 23	Absolute Bioavailabilities in Young and Elderly Males and Females with a 2 mg Tablet (Formulation F) - Study C92-058	27
Table 24	Effect of Food on Alosetron Absorption - Protocol S3BB1004	28
Table 25	Effect of Food on Alosetron Absorption - Protocol AS-03 - Japan	29
Table 26	<i>In Vitro</i> P450 Isozyme Metabolism of Alosetron	30
Table 27	Recovery for Metabolite U3 and Daughter Metabolites	32
Table 28	Recovery for Metabolite F1/ Monocarbonyl	33
Table 29	Pharmacokinetic metrics for alosetron and total radioactivity	34
Table 30	Suppression of 5-HT Induced Flare Response by IV Alosetron	36
Table 31	Alosetron 90 min Concentrations	38
Table 32	5-HT <sub>3</sub> Receptor Affinities for Alosetron and Metabolites	39
Table 33	Reported Circulating Concentrations of Alosetron and Metabolites	39
Table 34	Peak Mean Concentrations of N-Desmethyl-Alosetron after Single Doses in Japanese Males	40
Table 35	N-Desmethyl-Alosetron Mean Peak Concentrations	40
Table 36	Summary of Alosetron Metabolite Information	42
Table 37	P450 Inhibitory Potential of Alosetron	43
Table 38	Summary of Change in Probe-Drug Cocktail Ratios between Day -8 and Day 30	44
Table 39	Effect of Alosetron on Theophylline and Theophylline Metabolite Kinetics (CYPIA2)	46
Table 40	Pharmacokinetic Metrics for Levonorgestrel and Ethinyl Estradiol in Presence and Absence of Alosetron	47
Table 41	Haloperidol Pharmacokinetic Metrics in the Presence and Absence of Alosetron	47
Table 42	Cisapride Pharmacokinetic Metrics in Presence and Absence of Alosetron	49
Table 43	12 Hour Urinary 6 $\beta$ -Hydroxycortisol Excretion (mcgs) <sup>a</sup>	50
Table 44	Urinary 12 Hour 6 $\beta$ -Hydroxycortisol Excretion - Study S3BA1001*	51
Table 45	Pharmacokinetic Metrics in Young and Elderly with Multiple Dosing	53
Table 46	p-Values 1 <sup>st</sup> Dose Metrics vs. Day 28 Metrics	53
Table 47	Subject Demographics in Study GPK:90:01	53
Table 48	Pharmacokinetic Metrics of Alosetron in Young and Elderly Males - Study GPK:90:01	54
Table 49	Normalized Alosetron Pharmacokinetic Metrics with Age - Protocol GPK:90:01	54
Table 50	Alosetron Pharmacokinetic Metrics with Age After <i>Intravenous</i> Dosing - Protocol C92-058	55
Table 51	Alosetron Pharmacokinetic Metrics with Age After <i>Oral</i> Dosing - Protocol C92-058	55
Table 52	Normalized Alosetron Pharmacokinetic Metrics with Age - Protocol C92-058	56
Table 53	Studies with Pharmacokinetic Data in Women	57
Table 54	Pharmacokinetic Metrics in Male and Females after 57 Doses - Protocol S3BB1011	57
Table 55	Gender Effect on Alosetron Plasma Concentrations - Protocol S3B-102	58
Table 56	Gender Effects - Protocol C92-058	59

Table 57	Normalized Alosetron Pharmacokinetic Metrics with Age - Protocol C92-058	59
Table 58	Subject Demographics in Alosetron Renal Impairment Study	61
Table 59	Effect of Renal Insufficiency on Alosetron Pharmacokinetics	62
Table 60	Alosetron Population Pharmacokinetic Study - Subject Demographics	64

### List of Appendices

APPENDIX 1	Comparative Molar Doses and Exposure of Alosetron and Other Compounds	83
APPENDIX 2	Alosetron Metabolic Pathways	85
APPENDIX 3	Extent and Duration of Suppression of Flare Response by Alosetron	93
APPENDIX 4	Cortisol Production, Urinary 6-β-Hydroxycortisol Excretion, and Alosetron Exposure	97
APPENDIX 5	Dietary Inducers of CYP1A2	100

### List of Abbreviations

5-HT	5-Hydroxytryptamine (Serotonin)
6-β-OH-Cortisol	6-beta-hydroxycortisol
ACTH	Adenocorticotrophic Hormone
AE	Adverse Effect or Adverse Event
Ae	Amount eliminated in the urine
A <sub>ex</sub>	Amount eliminated in the urine through time X
ANOVA	Analysis of Variance
APCI/LC/MS/MS	Atmospheric Pressure Chemical Ionization / Liquid Chromatography / Mass Spectrometry / Mass Spectrometry
AUC <sub>a-b</sub>	area under the plasma-concentration-time curve from time a to time b
AUC <sub>b</sub>	area under the plasma-concentration-time curve from time 0 to time b
AUC <sub>m</sub>	area under the plasma-concentration-time curve for metabolites
AUC <sub>p</sub>	area under the plasma-concentration-time curve for parent compound
BW/O	Black/White/Oriental
BID	Bis In Diem (Twice daily)
BSA	Body Surface Area
CIE	Chemotherapy Induced Emesis
Cl	Clearance
Cl/F	Clearance determined after oral drug administration and uncorrected for absorption
Cl <sub>cr</sub>	Creatinine Clearance
Cl <sub>m</sub>	Clearance of Metabolite
Cl <sub>p</sub> or Cl <sub>p</sub>	Clearance of Parent Compound
C <sub>max</sub>	maximum measured concentration
C <sub>min</sub>	minimum measured concentration
CV	Coefficient of variation
DPEII	Division of Pharmaceutical Evaluation II
E <sub>h</sub>	Hepatic Extraction Ratio
F	Fraction of dose that's systemically bioavailable
F <sub>abs</sub>	Fraction of dose absorbed
F <sub>dose</sub>	Fraction of dose
F <sub>g</sub>	Fraction of dose available after first pass through the gastrointestinal mucosa
F <sub>h</sub>	Fraction of dose available after first pass through the liver
f <sub>m</sub>	Fraction Metabolized
FMO	Flavin Monooxygenase
FSH	Follicle Stimulating Hormone
F <sub>sys</sub>	Fraction of dose that's systemically bioavailable

Fsystemic.....	Fraction of dose that's systemically available after first pass
GI.....	Gastrointestinal
gluc or GLUC.....	Glucuronide
h or hr or hrs.....	hour or hours
HAPC.....	High Amplitude Propulsive Contractions
HCG.....	Human Chorionic Gonadotropin
IV.....	Intravenous
ka.....	Absorption rate constant
km.....	Rate constant for metabolism
kp.....	Rate constant for elimination of parent compound
L.....	Liter(s)
L/Hr.....	Liters per hour
LC/APCI/MS/MS.....	Liquid Chromatography - Atmospheric Pressure Chemical Ionization - Tandem Mass Spectrometry
LH.....	Luteinizing Hormone
LLOQ.....	lower limit of quantitation
LS.....	SAS geometric least squares
mcg/L.....	micrograms/Liter
M/F.....	Male/Female
MAO.....	Monoamine Oxidase
min.....	Minutes
n.....	Number of subjects/observations
NAT.....	N-Acetyltransferase
NAT1.....	N-Acetyltransferase 1
NAT2.....	N-Acetyltransferase 2
NDA.....	New Drug Application
nM or nM/L.....	nanomolar or nanomoles/Liter
NS.....	Not Significant
°C.....	Degrees Centigrade
OCPB.....	Office of Clinical Pharmacology and Biopharmaceutics
PK.....	Pharmacokinetic
PK-PD.....	Pharmacokinetic - Pharmacodynamic
PO.....	per os (by mouth)
qd.....	quinque diem (once daily)
Qh.....	Hepatic Blood Flow
RBC.....	Red Blood Cell
RP - HPLC - UV.....	Reverse Phase High Pressure Liquid Chromatography with Ultraviolet Detection
SD.....	Standard Deviation
SEE.....	Standard Error of the Estimate
Soln.....	Solution
t <sub>1/2</sub> .....	half-life
t <sub>1/2m</sub> .....	half-life of metabolites
t <sub>1/2p</sub> .....	half-life of parent compound
Tab.....	Tablet
t <sub>lag</sub> .....	Lag time for absorption
Tmax.....	Time to maximum concentration
USP.....	United States Pharmacopeia
UV.....	Ultraviolet
V/F.....	Volume of Distribution uncorrected for bioavailability
Vdβ.....	Volume of Distribution beta (Calculation based on clearance)
Vm.....	Mean Volume of Distribution of Metabolites
Vp.....	Volume of Distribution of Parent Compound
Vss.....	Volume of Distribution at Steady State
λz.....	Elimination Rate Constant for terminal elimination phase
μM.....	micromoles or micromoles/liter