CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-107

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

*New Drug Application*
*Clinical Pharmacology and Biopharmaceutics Review*

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| NDA: | 21-107 |
| Type of Submission: | NDA BM |
| Generic Name: | Alosetron HCl |
| Formulation(s); | Tablet - Immediate Release |
| Strength(s); | 1 mg |
| Route(s) | PO |
| Brand Name: | Lotronex™ |
| Sponsor: | Glaxo Wellcome, Inc.<br>Research Triangle Park, NC |
| Submission Date(s): | December 14, 1999 |
| Reviewer: | Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. |

## I. SYNOPSIS

Submission contains a list of Ongoing or Planned Alosetron Phase II, III, and IV Clinical Trials and a list of patient registries.

As submission contains only 'non-PK' data (i.e. no biopharmaceutic, pharmacokinetic, or pharmacodynamic assessments), no Clinical Pharmacology/Biopharmaceutics Review is needed for this submission.

## II. SIGNATURES

/S/

Ronald E. Kavanagh, BS Pharm, Pharm.D., Ph.D., OCPB/DPE-2

1-27-99
Date

/S/

David Lee, Ph.D., Team Leader OCPB/DPE-2

1/7/2000
Date

CC:

NDA 21-107 (orig., 1 copy)
HFD-180 (Prizont, Senior, Levine)
HFD-870 (ChenME, Lee, Kavanagh)
CDR (B.Murphy)

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

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| **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.<br>Research Triangle Park, NC |
| **Submission Date(s):** | June 29, 1999<br>August 23, 1999<br>September 10, 1999<br>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

/S/

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

Jan 06, 2000
Date

/S/

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

1/6/2002

Date

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

*New Drug Application*
*Clinical Pharmacology and Biopharmaceutics Review*

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## I. SYNOPSIS

Alosetron is a $5HT_3$ antagonist and the proposed indication is: **'LOTRONEX 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* Ki. (The Ki is the concentration required for 50% $5HT_3$ 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 $5HT_3$ 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 $5HT_3$ 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 Ki 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 $5HT_3$ receptor blockade is unclear. Most of the rest of the circulating metabolites were not identified and Ki's were not reported.

Another inconsistency that argues against the mechanism of action being mediated via $5HT_3$ 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 suprising 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 IA2, 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

expoxide 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 it's 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 is 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 Ki *in vivo* and the variability in exposure between subjects.

Due to localization of CYPIIIA4 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 possibilty of off label use of cisapride, which is metabolized by CYPIIIA4, 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 CYPIA2 metabolism of caffeine and NAT2 metabolism of dapsone. Formal *in vivo* drug interaction studies did not show inhibition of CYPIA2 metabolism of theophylline or CYPIIIA4 metabolism of other drugs. Based upon the data this reviewer does not believe there is a clinically significant inhibition of CYPIA2. 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 CYPIA2 include dietary and environmental factors such as safroles 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

## *List of Tables*

## *List of Appendices*



## *List of Abbreviations*

5-HT.....5-Hydroxytryptamine (Serotonin)
6-β-OH-Cortisol.....6-beta-hydroxycortisol
ACTH.....Adenocorticotropic Hormone
AE.....Adverse Effect or Adverse Event
Ae.....Amount eliminated in the urine
$Ae_X$.....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
AUCa-b.....area under the plasma-concentration-time curve from time a to time b
AUCb.....area under the plasma-concentration-time curve from time 0 to time b
*AUCm*.....area under the plasma-concentration-time curve for metabolites
*AUCp*.....area under the plasma-concentration-time curve for parent compound
B/W/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
Clcr.....Creatinine Clearance
*Clm*.....Clearance of Metabolite
Clp or *Clp*.....Clearance of Parent Compound
Cmax.....maximum measured concentration
Cmin.....minimum measured concentration
CV.....Coefficient of variation
DPEII.....Division of Pharmaceutical Evaluation II
Eh.....Hepatic Extraction Ratio
F.....Fraction of dose that's systemically bioavailable
$F_{abs}$.....Fraction of dose absorbed
Fdose.....Fraction of dose
Fg.....Fraction of dose available after first pass through the gastrointestinal mucosa
Fh.....Fraction of dose available after first pass through the liver
*fm*.....Fraction Metabolized
FMO.....Flavin Monooxygenase
FSH.....Follicle Stimulating Hormone
$F_{sys}$.....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 Chormatography - Atomospheric 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
$t_{1/2}$.....half-life
$t_{1/2}m$.....half-life of metabolites
$t_{1/2}p$.....half-life of parent compound
Tab.....Tablet
$t_{lag}$.....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