

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-107

MEDICAL REVIEW(S)

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS  
MEDICAL OFFICER REVIEW/

NDA: 21107

Sponsor: Glaxo Wellcome, Inc.

Drug: Alosetron Hydrochloride (Lotronex™) Tablets

Indication: Treatment of Irritable Bowel Syndrome (IBS)

Date Received by the DGICDP: July 1, 1999.

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Medical Officer: Dr. Robert Prizont, M.D.

**Abstract.** Alosetron hydrochloride is a novel drug that competes with 5-HT<sub>3</sub> serotonin receptor sites; 5-HT<sub>3</sub> serotonin receptor sites are distributed throughout the gastrointestinal nerve terminals and may relax or increase motility of the gastrointestinal tract. In this NDA the sponsor included clinical data to support a label claim of alosetron hydrochloride tablets, 1 mg b.i.d. for the treatment of irritable bowel syndrome (IBS) in women with diarrhea predominance. In two separate pivotal multicenter, randomized, double-blind, placebo-controlled clinical trials, enlisted investigators randomized 1273 women with mild to moderate IBS to alosetron or placebo. Both trials were conducted under identical protocol. The primary efficacy endpoint was the adequate relief of IBS abdominal pain/discomfort. Treatments were given for a period of 3 months. In both studies, alosetron 1 mg b.i.d., showed statistically significant superiority over placebo in the adequate relief of IBS abdominal pain/discomfort in women treated for a combined 3 month period. Alosetron was also superior in improving lower bowel functions, i.e., stool consistency and stool frequency. In *post-hoc* analyses, the sponsor claimed efficacy was driven by a subset of IBS patients enrolled by investigators with a IBS subtype defined by the sponsor as diarrhea-predominant. This clinical review describes the results of both pivotal trials and discusses the findings in light of the submitted results, the Rome diagnostic criteria guidelines recommended by the American Gastroenterological Association, and FDA guidelines on efficacy in clinical trials.

## TABLE OF CONTENTS

|   |    |
|---|----|
| DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS .....  | 1  |
| MEDICAL OFFICER REVIEW . ABSTRACT .....   | 1  |
| 1. INDICATION AND DOSAGE .....  | 4  |
| 2. BACKGROUND .....   | 4  |
| 1.1 Brief Summary of Pharmacologic Class of Drug, Chemistry, and Pharmacokinetics of<br>Alosetron Hydrochloride. .... | 4  |
| 1.1.1 Chemistry.....  | 4  |
| 1.1.2 Pharmacology .....  | 5  |
| 1.1.3 Pharmacokinetics.....   | 6  |
| 1.2 Reviewer Comments.....  | 7  |
| 1.3 BRIEF SUMMARY REVIEW OF IRRITABLE BOWEL SYNDROME. ....  | 9  |
| 3. CONTROLLED CLINICAL TRIALS .....   | 11 |
| 1.4 PIVOTAL TRIAL S3BA3001.....   | 11 |
| 1.4.1 Protocol.....   | 11 |
| 1.5 Descriptive of Trial S3BA3001 .....   | 16 |
| 1.5.1 Patient Disposition.....  | 16 |
| 1.5.2 Demographics.....   | 18 |
| 1.5.3 Primary Efficacy Results.....   | 18 |
| 1.5.4 Secondary Efficacy Results.....   | 22 |
| 1.5.5 Reviewer Comments.....  | 24 |
| 1.6 PIVOTAL TRIAL SB3A3002.....   | 31 |
| 1.6.1 Protocol.....   | 31 |
| 1.7 Descriptive of Trial S3BA3002.....  | 31 |
| 1.7.1 Patient Disposition.....  | 31 |
| 1.7.2 Demographics.....   | 33 |
| 1.7.3 Primary Efficacy Results.....   | 33 |
| 1.7.4 Secondary Efficacy Results .....  | 36 |
| 1.7.5 Reviewer Comments.....  | 38 |
| 1.8 Dose-Ranging Study S3B2001.....   | 40 |
| 1.8.1 Protocol.....   | 40 |
| 1.9 Descriptive of Trial SB3A2001.....  | 42 |
| 1.9.1 Disposition of Patients.....  | 42 |
| 1.9.2 Demographics .....  | 43 |
| 1.9.3 Primary Efficacy Results.....   | 44 |
| 1.9.4 Secondary Efficacy Parameters .....   | 45 |
| 1.9.5 Reviewer Comments.....  | 46 |
| 4. Reviewer Summary on Alosetron Efficacy in IBS Trials.....  | 46 |
| 1.10 Pivotal Clinical Trial A3001 and A3002.....  | 46 |
| 1.10.1 . Intention-to-Treat.....  | 46 |
| 1.10.2 . IBS Subtypes.....  | 48 |
| 5. Recommendations For Regulatory Actions.....  | 48 |
| APPENDIX 1.....   | 50 |
| Trial A3001. List of Prohibited Concurrent Medications.....   | 50 |
| APPENDIX 2.....   | 54 |

|   |    |
|---|----|
| Trial A3001. Women with Menses versus Women without Menses..... | 54 |
| APPENDIX 3.....   | 58 |
| Trial A3001. Weekly Relief of Abdominal Pain/Discomfort.....    | 58 |
| APPENDIX 4.....   | 62 |
| Trial A3001. Patient Rating of Abdominal Pain/discomfort .....  | 62 |
| APPENDIX 5.....   | 72 |
| Fibromyalgia Subset (A3002).....                                | 72 |
| APPENDIX 6.....   | 75 |
| Trial A3002. Patient Rating of Abdominal Pain/Discomfort .....  | 75 |
| APPENDIX 7.....   | 80 |
| Trial A3002. Stool Consistency.....                             | 80 |
| APPENDIX 8.....   | 85 |
| Trial A3002. Stool Frequency.....                               | 85 |

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## 1. INDICATION AND DOSAGE

In its proposed label, Glaxo included the following indication and dosage for administration of alosetron tablets.

**INDICATIONS AND USAGE:** LOTRONEX is indicated for the treatment of irritable bowel syndrome (IBS) in female patients with diarrhea predominance.

### DOSAGE AND ADMINISTRATION:

**Usual Dose in Adults:** The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food.

The effectiveness of LOTRONEX in females (18 years of age and older) was demonstrated in two placebo-controlled studies in which 1 mg was given twice daily for 12 weeks. Efficacy in males has not been established.

Safety of continuous treatment has been established in females and males for periods up to 6 months.

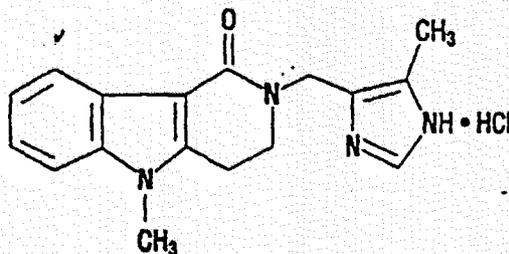
**Pediatric Patients:** No studies have been conducted in patients less than 18 years of age.

## 2. BACKGROUND.

### 1.1 *Brief Summary of Pharmacologic Class of Drug, Chemistry, and Pharmacokinetics of Alosetron Hydrochloride.*

#### 1.1.1 Chemistry

In this NDA, Glaxo Wellcome submitted data to support safety and effectiveness of alosetron hydrochloride for the treatment of irritable bowel syndrome (IBS). Alosetron was first synthesized by Glaxo in 1987. The chemical structure is the following:



## 1.1.2 Pharmacology

- *Note from the Reviewer. This section of Pharmacology will include brief overview summaries of relevant information on experimental studies conducted by the sponsor on the pharmacokinetics and pharmacology of alosetron. It is not intended to provide a comprehensive review of alosetron pharmacokinetics and pharmacology. Thus, no details on methodology or experimental design will be included in my description or comments on experimental studies. The reader is referred to the biopharmaceutical and pharmacology reviews written by Dr. Ron Kavanagh, Ph.D., and Dr. Ke Zhang for detail descriptive and commentary on alosetron pharmacokinetics and experimental pharmacology.*

Pharmacologically, alosetron exerts its activity by competing with systemic serotonin on HT<sub>3</sub> serotonin receptor sites. 5-HT<sub>3</sub> receptors are widely distributed within the sensory and enteric neurons of the human gastrointestinal tract as well as in the spinal cord and brain. Their activation leads to contraction or relaxation of gastrointestinal smooth muscle thereby affecting gut motility. Like other 5-HT<sub>3</sub> receptor antagonists, i.e, ondansetron, alosetron delays colonic transit time. In IBS patients, alosetron appears to selectively delay left colonic transit time, as illustrated in the next table. In this Glaxo study, alosetron, 2 mg, b.d., was given to a group of 12 IBS males and females for a period of eight days, (taken from the recent Gunput's review<sup>1</sup>).

|  | Placebo      | Alosetron    | P     |
|--|--------------|--------------|-------|
| Colonic transit (h), median (range)              | 38<br>(1-67) | 49<br>(1-72) | 0.07  |
| Right colonic transit (h), median (range)        | 7<br>(1-23)  | 7<br>(0-31)  | 0.57  |
| Left colonic transit (h), median (range)         | 12<br>(0-23) | 23<br>(0-52) | 0.006 |
| Rectosigmoid colonic transit (h), median (range) | 8<br>(0-24)  | 5<br>(0-23)  | 0.38  |

*Note:* Whole gut transit time (WGT) was measured by radio-opaque polyethene markers ingested for 3 consecutive days. Small bowel transit time (SBT) was measured by a breath H<sub>2</sub>-generating meal. Colonic transit time was calculated by the difference of WGT-SBT.

- At doses of 0.25 mg b.i.d. and 4 mg b.i.d., alosetron significantly increases colonic compliance. Pharmacological investigations in healthy subjects and IBS patients, revealed that alosetron increased prandial colonic motility (frequency and amplitude of contractions) in IBS subjects and healthy volunteer subjects but had no effect on small bowel motility in healthy volunteers. Alosetron did not affect bloating in IBS patients.
- In a randomized, double-blind, placebo-controlled study in 7 healthy males, alosetron, 4 mg single dose, significantly increased absorption of sodium and water in the jejunum.
- Relevant to IBS as a functional bowel disorder with a psychological component, the sponsor reported that "an initial study with scopolamine (GHP:89:37) in healthy males provided data on cognitive indices to allow sample size calculations for future studies but no formal analysis of the data was conducted".

- Pertinent to the apparent predominant effect of alosetron on IBS female patients, is the possible interaction of alosetron with female hormones such as estradiol. Glaxo noted that *"the effect of alosetron on the pharmacokinetics of levonorgestrel and ethinyl estradiol was examined in S3BA1002 in healthy female subjects when administered alone for 21 days, and following co-administration of alosetron 1mg BID orally for 21 days. Another objective of the investigation was to examine the effect (of alosetron) on serum luteinizing hormone (LH) as a pharmacodynamic measure of efficacy. A pharmacodynamic effect could not be determined due to inadequate sampling; however, the incidence of breakthrough bleeding was similar in both treatment periods suggesting no effect"*.

### 1.1.3 Pharmacokinetics

Pharmacokinetic studies conducted by Glaxo revealed that after oral administration, alosetron was rapidly absorbed; bioavailability was approximately 60%. Plasma concentration was higher and more variable in females than in males. This gender difference in plasma concentration was due to lower clearance of alosetron in females. Gender differences in alosetron clearance and in plasma concentration reached statistical significance when comparing elderly males and females. Similarly, volume of distribution was 20-25% lower in females than in males, at any age. This gender differences are shown in the next table, taken from Gunput' review article.

Table 1. Pharmacokinetics of alosetron (mean, SD)

|                    | AUC<br>(ng/ml/h) | C <sub>max</sub><br>(ng/ml) | T <sub>max</sub><br>(h) | T <sub>1/2</sub><br>(h) | Cl <sub>s</sub><br>(ml/min) | Vd <sub>d</sub><br>(L) |
|--------------------|------------------|-----------------------------|-------------------------|-------------------------|-----------------------------|------------------------|
| Males < 65 years   |                  |                             |                         |                         |                             |                        |
| IV                 | 49.8 (11.3)      | 42.7 (12.8)                 | 0.26 (0.02)             | 1.5 (0.25)              | 703 (167)                   | 84 (18)                |
| PO                 | 26.6 (10.1)      | 10.3 (3.5)                  | 1.08 (0.39)             | 1.4 (0.24)              |                             |                        |
| Females < 65 years |                  |                             |                         |                         |                             |                        |
| IV                 | 70.6 (38.2)      | 45.3 (14.0)                 | 0.27 (0.05)             | 1.6 (0.40)              | 583 (261)                   | 67 (20)                |
| PO                 | 41.9 (32.8)      | 14.3 (7.7)                  | 1.04 (0.42)             | 1.5 (0.41)              |                             |                        |
| Males > 65 years   |                  |                             |                         |                         |                             |                        |
| IV                 | 52.2 (12.3)      | 51.7 (8.1)                  | 0.25 (0.00)             | 1.7 (0.20)              | 674 (172)                   | 85 (15)                |
| PO                 | 28.1 (11.6)      | 10.8 (4.4)                  | 0.98 (0.46)             | 1.6 (0.21)              |                             |                        |
| Females > 65 years |                  |                             |                         |                         |                             |                        |
| IV                 | 78.8 (24.0)      | 64.5 (17.0)                 | 0.25 (0.00)             | 1.8 (0.31)              | 461 (123)                   | 63 (13)                |
| PO                 | 54.6 (27.7)      | 19.5 (8.9)                  | 0.83 (0.27)             | 1.7 (0.36)              |                             |                        |

- In a 12-week controlled-clinical study, alosetron pharmacokinetics was investigated in 215 IBS patients (55=Males; 149=Females). Oral alosetron tablets were administered in ascending doses from 1mg up to 8 mg per day. Similar to healthy subjects, gender differences in alosetron clearance were noticeable in IBS patients; clearance was 27% lower in IBS females than in IBS males. Gender differences in alosetron clearance remained invariable during the 12-week study, and were not influenced by body weight, age, diet, race, hormonal contraceptives and, were minimally influenced by alosetron dose (Study S3BA2001, Report GM1997/00189/00).
- The principal route of alosetron elimination is metabolic transformation by liver microsomal cytochrome P<sub>450</sub> (CYP) enzymes (2C9, 3A4, 1A2). Approximately 94% of absorbed

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alosetron is metabolized by liver CYP enzymes. The sponsor notes that because alosetron is metabolized by a variety of CYP enzymes, it is unlikely to be vulnerable to inhibition or induction of any one enzyme by the other. In vivo studies revealed no inneraction with cisapride, haloperidol, an estrogen representative, and mild interaction with caffeine. Glaxo reports that administration of radiolabeled alosetron to an individual resulted in recovery of 13 metabolites from the urine. The 6-hydroxy and the bis-oxidized metabolites were found in largest proportions (15% and 14%, respectively). With normal renal clearance, about 6% of absorbed alosetron is eliminated in the urine. Alosetron metabolites are partly in feces,  $\pm 30\%$ . There are no reports on bile elimination of alosetron or its metabolites.

## 1.2 Reviewer Comments.

The following pharmacological-pharmacokinetic issues might be of clinical relevance:

1. As cited by Gunput in his review article, oral administration of alosetron at higher doses than the recommended in the proposed label revealed a significant delay in left colonic transit time in IBS patients administered alosetron. The article did not specify whether gender differences or female hormones contributed to this particular pharmacological action of alosetron.

In a study published in 1996, Degen and Phillips<sup>2</sup> evaluated colonic transit time in 20 healthy male and 12 healthy women ranging from 19 to 45 years of age. Whole gut transit time and colonic transit time were evaluated by non-invasive scintigraphy and radio-opaque markers (radio-opaque markers contained in a capsule were administered for four days; subsequent to the ingestion of radio-opaque markers, the scintigraphy method was began by administration of pellets labeled with <sup>111</sup>In Cl<sub>3</sub>. The radioactive pellets were administered orally to fasting volunteers. The capsule dissolved in the ileocecal region and thereafter marked ileocecal transit and colonic transit of contents). Colonic transit time was evaluated in women during both, the follicular and luteal phases. As seen in the next schematic representation, colonic transit time was significantly lower in healthy women as compared to healthy men. Although women menstrual cycle appeared to widen further this difference, this latter comparison was not statistically significant, in part due to large intrinsic variability and the small change effected by menstrual hormones. The next two figures exemplify these results.

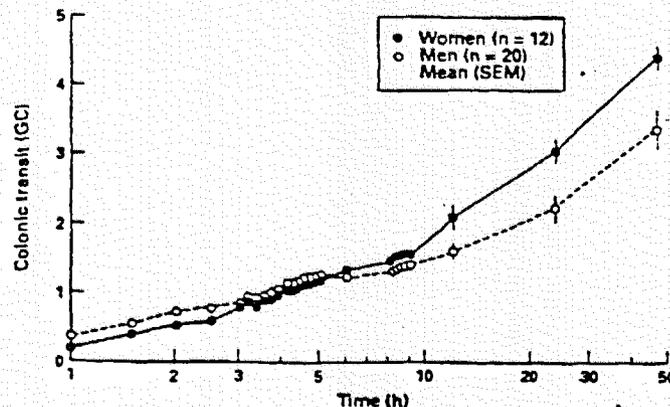


Figure 4: Sex differences in colonic transit, expressed as the progression of the geometric centres of scintigraphic markers against time. High values for the GC, signifying faster colonic transit, become apparent in men after 12 hours (approximately). At that time the GC was approximately 2.0 indicating that the centre of contents was in the transverse colon.

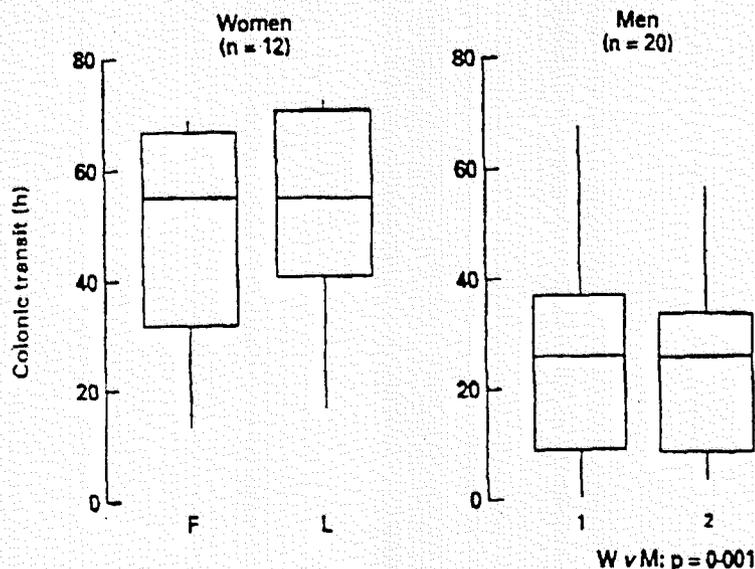
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Figure 3: Total colonic transit as measured by the radio-opaque marker method, in healthy men and women, shown as median values (bars), interquartile ranges (boxes), and range for men and women. Women were studied in the follicular (F) and luteal (L) phases of the menstrual cycle. Men were studied twice, 14 days apart. Colonic transit was significantly faster in men at 24 hours.

In view of the results of reported slower colonic transit time in females, it might be of relevance to ascertain whether administration of alosetron to females and males, in alosetron doses which would include 1 mg b.i.d., enhances or diminishes gender gap on colonic transit time.

2. Noticeable in the above table of alosetron pharmacokinetics in males and females younger than 65 years also reported in Gunput's review article, was a gender difference in some relevant PK parameters, i.e., lower clearance of alosetron in females <65 years after intravenous infusion, associated with a higher AUC revealed in the same group of females.

In a randomized, open-label, two-way, crossover study titled "An Investigation of the Gender Differences in the Pharmacokinetics of Alosetron", Glaxo investigated the effect of gender and age in four groups (n=12 each) of young (18-40 yrs) and elderly (>65 yrs) male and female healthy subjects. All subjects received 2 mg/days/single dose alosetron by either intravenous infusion or as an oral dose (GW submitted summary does not specify if the 2 mg alosetron was given as a single dose or by administering 1 mg b.i.d.), Page 166, Vol. 1. As seen in the next Glaxo table, administration of intravenous alosetron resulted in lower clearance in females, phenomenon observed across all ages. The gender difference of higher alosetron AUC after an oral 2 mg dose was observed between males and females > 65 yrs. Young females (18-40 yrs) had similar AUC than young males. A similar trend was observed in the alosetron plasma concentrations ( $C_{max}$ ) of young and elderly females. These results, together with the aforementioned pharmacokinetic results reported by Gunput in females younger than 65 years, suggest that the gap between males and females in some of the alosetron pharmacokinetic parameters, i.e., higher AUC and  $C_{max}$  in females, is initially observed in women older than 40 yrs and continues to increase with age.

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**Table 6.17. Alosetron Pharmacokinetic Parameters (Protocol C92-058)**

| Parameter*                      | Route | Young Males      | Young Females            | Elderly Males    | Elderly Females                |
|---------------------------------|-------|------------------|--------------------------|------------------|--------------------------------|
| C <sub>max</sub><br>(ng/mL)     | IV    | 40.2 (22.7-68.2) | 44.6 (29.4-67.7)         | 49.8 (38.2-67.7) | 62.8 (32.2-98.6) <sup>b</sup>  |
|                                 | PO    | 9.4 (3.6-15.0)   | 12.0 (2.8-28.1)          | 9.8 (4.9-19.7)   | 17.2 (4.3-34.0) <sup>c</sup>   |
| t <sub>max</sub><br>(h)         | IV    | 0.25 (0.25-0.33) | 0.25 (0.25-0.42)         | 0.25 (0.25-0.25) | 0.25 (0.25-0.25)               |
|                                 | PO    | 1.00 (0.75-2.00) | 1.00 (0.50-2.00)         | 0.75 (0.50-2.00) | 0.75 (0.50-1.50)               |
| AUC <sub>0-∞</sub><br>(ng·h/mL) | IV    | 49.4 (34.5-65.5) | 61.3 (30.6-159.2)        | 52.2 (30.3-73.7) | 74.1 (50.8-129.3) <sup>a</sup> |
|                                 | PO    | 24.8 (11.0-42.2) | 30.5 (6.9-119.9)         | 26.5 (10.8-51.5) | 47.1 (14.2-111.8)              |
| t <sub>1/2</sub><br>(h)         | IV    | 1.5 (1.2-1.9)    | 1.8 (1.3-2.4)            | 1.7 (1.4-2.0)    | 1.8 (1.5-2.4)                  |
|                                 | PO    | 1.4 (1.0-1.7)    | 1.4 (1.0-2.2)            | 1.6 (1.3-1.9)    | 1.7 (1.1-2.4) <sup>b</sup>     |
| CL (mL/min)                     | IV    | 675 (509-967)    | 544 (209-1089)           | 639 (452-1100)   | 450 (258-656) <sup>c</sup>     |
| V <sub>ss</sub> (L)             | IV    | 82 (69-122)      | 65 (47-109) <sup>c</sup> | 83 (66-122)      | 62 (46-94) <sup>c</sup>        |
| F                               |       | 0.50 (0.27-1.03) | 0.49 (0.20-0.95)         | 0.51 (0.35-0.70) | 0.63 (0.28-0.87)               |

\* geometric LS mean (range) except t<sub>max</sub>: median (range), n=12

<sup>b</sup> significantly different from young subjects of same gender (age-related differences)

<sup>c</sup> significantly different from males of similar age (gender-related differences)

3. Serotonin 5-HT<sub>3</sub> receptor antagonists have been investigated as potential therapeutic drugs for use in clinically common CNS disorders such as depression and anxiety<sup>3</sup>. The findings of studies with 5-HT<sub>3</sub> receptor antagonists on CNS disorders appear incomplete, largely because an absence of randomized, double-blind, placebo-controlled trial designs proving efficacy of 5-HT<sub>3</sub> receptor antagonists in CNS affective disorders. IBS patients tend to have an associated psychological component. It would have been relevant to have had a better knowledge and understanding about the action of alosetron on a variety of CNS disorders, particularly affective disorders. Noteworthy to the gender differences in the proposed therapeutic IBS indication, is the finding of gender differences in the rate of synthesis of brain serotonin. Using positron emission tomography a group of neurobiologists and psychiatrists from McGill University found that healthy young women have a 52% lower synthesis rate of serotonin in the brain<sup>4</sup>. The authors postulated that this markedly lower serotonin synthesis in the female brain may be a relevant factor in the higher incidence of unipolar depression in females.

### 1.3 BRIEF SUMMARY REVIEW OF IRRITABLE BOWEL SYNDROME.

In the US, IBS has a prevalence ranging from 9.4% to 19.5%. Women have a higher prevalence than men, e.g. up to 24%; the prevalence is similarly higher in whites, and in individuals younger than 50-60 years<sup>5,6</sup>. The actual incidence of IBS is still unclear, with estimates varying between 1% to 2.9%. According to a national US survey, IBS accounts for an estimated 2.4-3.5 physician visits per year which results in an estimated 2.2 million prescriptions per year<sup>7</sup>.

In 1986, the organizers of the XIII International Congress of Gastroenterology established a working team to develop guidelines for the *diagnosis* of irritable bowel syndrome<sup>8</sup>. The working team met in Rome in 1987, and presented the final draft in September of 1988. As stated by this team, the guidelines emphasize a *positive diagnosis*, rather than the *exhaustive use of tests to exclude other diseases*. In 1997, the Patient Care Committee of the American Gastroenterological Association (AGA) officially endorsed the Rome Criteria for the diagnosis of IBS. According to the official AGA recommendation<sup>9</sup>, IBS is defined as a *combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities, which is attributed to the intestines and associated with symptoms of pain and disturbed defecation and/or symptoms of bloatedness and distension*. In conjunction with these

gastrointestinal symptoms, the majority of IBS patients seeking medical treatment have associated clinically diagnosable psychological mood disorders such as depression or anxiety or exhibit a history of psychosocial trauma, e.g., sexual abuse. A relevant role of the CNS in IBS is supported by independent observations, as described by Mayer et al<sup>10</sup> in their article review on brain-gut interactions, e.g. a large number of IBS patients relate the onset of the disease to a stressful life event, give a history of "sensitive stomach" or intestines dating back to adolescence, and, behavioral psychotherapy and/or psychotropic mood-altering drugs such as antidepressants are "frequently effective in symptom relief".

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### 3. CONTROLLED CLINICAL TRIALS.

- Glaxo submitted two pivotal clinical trials to support the claim of alosetron efficacy in the treatment of women affected by irritable bowel syndrome. These two pivotal clinical trials were conducted under Protocols S3BA3001 and S3BA3002, respectively. In this section, I will summarize each of these protocols, and provide a descriptive on demographics, disposition and efficacy results of patients randomized to each of the two pivotal trials. Thereafter, and for each individual pivotal trial, I will include my comments. Subsequent to the description and comments of the two pivotal studies, I will briefly describe and comment the Phase II dose-ranging study, S3BA2001, conducted in the US and Canada.

#### 1.4 PIVOTAL TRIAL S3BA3001.

##### 1.4.1 Protocol.

The original prospective protocol was completed on July 9, 1997.

*i. Design.* The protocol stated that this will be an 18 week multi center, randomized, double-blind, parallel placebo-controlled study of alosetron in female subjects with irritable bowel syndrome. The protocol called for a randomization of 600 IBS women to be enrolled in approximately 125 ambulatory care centers/hospitals and private physician offices throughout the United States. According to the prospective protocol, the study is composed of 3 consecutive phases. They are as follows:

- A 2-week Screening Phase. To be included in this 2-week Screening Phase patients were required to fulfill the Rome Criteria for the IBS diagnosis, defined as follows (scanned-copied from the protocol):

1. At least 6 months of recurrent symptoms of the following:

a) Abdominal pain/discomfort which is: (at least one of the following must be present)

- relieved with defecation
- And/or associated with a change in stool frequency
- And/or associated with a change in stool consistency

AND

b) Two or more of the following, at least 2 days per week:

- Altered stool frequency (defined as > 3 bowel movements/day or < 3 bowel movements per week)
- Altered stool form (lumpy/hard or loose/watery)
- Altered stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

During the 2-week Screening Phase, patients had to satisfy the following criteria in order to be randomized and included in the 12-week treatment phase:

- documented the presence of abdominal pain and discomfort with an overall average pain and discomfort severity score between 1.0 and 3.3. Pain and discomfort severity was rated as 1 = mild, 2 = moderate, 3 = intense, and 4 = severe. For purposes of analysis, 'no pain' was assigned a score of zero. Overall average pain and discomfort severity scores were calculated from the daily telephone data entry of abdominal pain and discomfort.
- documented an average stool consistency score of  $\geq 2.5$ . Stool consistency was rated as 1 = very hard, 2 = hard, 3 = formed, 4 = loose, and 5 = watery.
- recorded at least 12 days of daily self-assessments.

The investigator was informed of the subjects' eligibility to continue into the Treatment Phase of the study via the touch-tone telephone data entry system.

In addition to the above criteria, screening included a complete physical, hematology and serum chemistries, a negative HCG and thyroid test, a sigmoidoscopy or colonoscopy (If not available in the prior 5 years), stool for ova and parasites, a lactose breath test, and fiber intake evaluation.

Patients who met the described screening criteria and passed the physical, laboratory evaluation and endoscopy, were included in the next phase of the study;

- **A 12-week Treatment Phase.** In accordance to the protocol, eligible IBS women would be randomized to either alosetron 1 mg b.i.d., or placebo and treated for a period of 12 weeks. Patients were supposed to record daily abdominal pain/discomfort, stool frequency and consistency. The investigator would be informed of the patient eligibility and continuation in the treatment by the telephone data entry system.
- **A 4-week Post Treatment Phase (28 $\pm$ 4 days).** This was prospectively established follow-up period, in which, patients would continue to record their abdominal symptoms until they receive the final telephone call.

*ii. Inclusion Criteria.* Patients would meet the inclusion criteria if:

Are female.

At least 18 years of age.

Are an ambulatory outpatient. Ambulatory is defined as not depending exclusively on a wheelchair for mobility. Nursing home subjects may be enrolled provided they are ambulatory. Subjects with spinal cord injuries resulting in paraplegia may not be enrolled.

Patients must also have had a lower endoscopic examination within the last 5 years. The type and length of the lower endoscopic would depend on the age of the patient, as the protocol specifies in the following paragraphs.

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- For subjects less than 50 years of age, flexible sigmoidoscopy after the onset of their IBS symptoms and within 5 years prior to the randomization visit, using a flexible sigmoidoscopy scope of 60cm.
- For subjects 50 years and older, a full colonoscopy (full colonoscopy using a scope of  $\geq 180$ cm, visualizing the cecum) or an air contrast (double contrast) barium enema plus a flexible sigmoidoscopy, after the onset of their IBS symptoms and within 5 years of the randomization visit.

### iii. Exclusion Criteria.

If, in the opinion of the examining physician, an unstable cardiovascular, renal, hepatic, pulmonary, endocrine, metabolic, hematologic, or gastrointestinal condition is present.

Evidence of a biochemical or structural abnormality of the digestive tract; these conditions include (but are not limited to):

- current evidence or history of inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- diverticulitis
- duodenal ulcer
- erosive esophagitis
- gastric ulcer
- gastroparesis
- gastrointestinal malignancy
- gastrointestinal obstruction
- carcinoid syndrome
- pancreatitis
- cholelithiasis
- amyloidosis
- ileus
- gastrointestinal surgery (exceptions: appendectomy, cholecystectomy, benign polypectomy, and hiatal hernia)
- A history or current evidence of laxative abuse (in the clinical judgment of the physician)
- Diagnosis of Symptomatic Gastroesophageal Reflux Disease, not controlled by a stable dose of medication.
- Diagnosis of Symptomatic Hiatal Hernia, not controlled by a stable dose of medication.

A major psychiatric disorder (DSM-III-R or DSM-IV), including major depression, psychoses, alcohol or substance abuse within the past 2 years.

Hepatic dysfunction [ALT (SGPT) or AST (SGOT) > 2.5 times the upper limit of normal].

Abnormal thyroid stimulating hormone (TSH). (If not done within the previous 12 months must be completed by day of randomization.)

Renal impairment (serum creatinine > 2.0mg/dl).

Any evidence of or treatment of malignancy (other than localized basal cell, squamous cell skin cancer or cancer in situ that has been resected) within the previous five years.

In addition, patients be not pregnant, lactating and if able to conceive, use appropriate means of contraception, e.g., oral birth control pills, progesterone implants, IUDs, abstinence.

*iv. Prohibited Concomitant Medications.* According to the protocol (original and amended) patients should be off theophylline, warfarin, antipsychotic drugs, anticholinergics, GI drugs, prokinetic drugs, laxatives, enemas, NSAIDs, narcotics for at least 7 days prior to entry in the study and for the remaining of the trial.

*The Complete List of Prohibited Concurrent Medications (pages 74-76, Vol. 158) is Included as Appendix 1 (of this review).*

*v. Allowed Concomitant Medications.* The following medications were allotted, provided patients were on a stable dose 30 days prior to screening:

- Antianginals (calcium channel blockers, nitrates)
- Antidepressants
- Antihypercholesterolemics (except cholestyramine)
- Antihyperglycemics (oral sulfonylureas)
- Antihypertensives ( $\beta$ -blockers,  $\alpha$ -blockers)
- Anxiolytics
- Bulking agents
- Pancreatic enzymes
- Thyroid replacement therapy (e.g. levothyroxine)

*vi. Primary Efficacy Measure or Endpoint.* The protocol states that primary efficacy measure or endpoint is *the adequate relief of IBS/pain discomfort*. It also states that patients will be asked the following question: *"In the last 7 days, have you had adequate relief of your Irritable Bowel Syndrome pain or discomfort?"*; acceptable patient responses should be (yes/no).

The protocol adds that the primary analysis will be the following:

The proportion of subjects with adequate relief of abdominal pain on at least 2 weeks/month is the primary efficacy parameter in this study. Adequate relief of IBS pain will be recorded weekly via the touch-tone data entry system and the proportion of subjects with adequate relief of abdominal pain/discomfort on at least 2 weeks/month, i.e., "monthly responders," will be calculated at Months 1, 2, and 3 (i.e., Month 1 = Weeks 1-4, Month 2 = Weeks 5-8, and Month 3 = Weeks 9-12, respectively).

The protocol also includes *"supportive analyses"* of the primary efficacy measure. The most relevant are the following:

**(a) Adequate Relief of IBS/Discomfort over the 12-week Treatment Period.** A patient is a treatment responder if she reports adequate relief for at least 6 of the 12 weeks during the treatment phase.

**(b) Correlation Between Weekly Adequate Relief of IBS Pain/Discomfort and Other Weekly Efficacy Measures.** This analysis was included to validate adequate relief of IBS pain/discomfort in relation the other efficacy parameters, i.e., pain severity, stool consistency, stool frequency, proportion of days with urgency, incomplete evacuation and bloating.

**(c) Subgroup Analyses.** On Page 39, in the section of primary efficacy measures, the protocol notes that where possible, the sponsor will assess the effects of age, race, hormone use, baseline stool consistency (scores of 2.5-3.5, >3.5), changes in fiber intake, and menstruation on the primary efficacy measure.

vii. **Secondary Efficacy Measures or Endpoints.** Included in the protocol are the following relevant secondary efficacy measures or endpoints:

**(a) Proportion of Pain/Discomfort Free Days.** According to the protocol, a "monthly responder" for the proportion of pain/discomfort-free days is defined by at least 50% pain/discomfort free days in months with at least 14 days pain assessments (via touch-tone data entry system). Months with 1-13 daily pain assessments, or with <50% proportion of pain-free days will be considered non-responders.

**(b) Lower GI Functions.** Stool consistency at baseline (13-day screening period) and at Months 1, 2, and 3, using the Last Observation Carried Forward imputation for missing data (LOCF). Other lower GI function of relevance in IBS will be analyzed, i.e., stool frequency, sense of urgency, bloating, and sense of incomplete evacuation.

**(c) Psychological Distress Evaluation – Anxiety (and Depression).** The protocol establishes that each patient should be administered at randomization and at the Final Visit a Symptom Checklist-90-Revised (SCL-90<sup>®</sup>), which consist of 90 questions to assess psychological distress. The patient responses indicate the degree of distress for the past seven days using the following score: 0=not at all, 1=little bit, 2=moderately, 3=quite a bit, 4=extremely.

The psychological distress scores will be summarized in following three global indices of distress: Global Severity Index (GSI), Positive Symptom Distress Index (PSDI), Positive Symptom Total (PST).

**(d) Quality of Life (QOL) Measures.** The y encompass the Irritable Bowel Syndrome Quality of Life (IBSQOL) questionnaire, a 30-item quality of life questionnaire, and the SF-36, a 36-item general health related quality of life questionnaire.