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Alosetron in Irritable Bowel Syndrome

Strategies for its Use in a Common Gastrointestinal Disorder

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Abstract

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterised by recurrent abdominal pain and altered bowel habits in the absence of any discernible structural, biochemical and physiological abnormalities. Although there is no specific biological marker for the diagnosis of this disorder, recently developed symptom-based criteria provide the tools necessary to make a diagnosis. The precise underlying pathophysiology of IBS remains unknown. However, disturbances in the brain-gut axis involving the central nervous system and the enteric nervous system have emerged as an underlying concept for IBS. In this regard, conventional treatment has been recognised as unsatisfactory for many patients with IBS and novel, neuroenteric modulatory compounds have been introduced for use by clinicians. Specifically, compounds interacting with the 5-hydroxytryptamine (5-HT, serotonin) receptors of the 5-HT_3 and 5-HT_4 subtype have been demonstrated of benefit in some patients for the treatment of IBS.

In this leading article, we present the current data on the pharmacology, clinical trials, indications and adverse effects of alosetron, a potent and selective 5-HT_3 antagonist. As a result of the recognition of serious adverse effects, the indication for alosetron has been restricted and it is now indicated only for women with severe diarrhoea-predominant IBS who have symptoms for at least 6 months and who have failed to respond to conventional therapy. Prescribing restrictions and the risk-management programme implemented as required by the US FDA is reviewed along with a summary of the studies to be performed after reintroduction of alosetron to monitor safety.

Irritable bowel syndrome (IBS) is a frequent yet little understood disorder which affects 10–20% of the adult population. Approximately 70% of patients with IBS are female. Patients present to family

doctors, gastroenterologists, surgeons and gynaecologists with recurrent abdominal discomfort associated with altered bowel habits and often with bloating. IBS diminishes quality of life and significantly impacts on direct healthcare expenditures.[1,2] The total costs of IBS are approximately $US30 billion in the US each year, including both direct medical costs and indirect costs such as lost work time or lowered productivity.[3]

Several underlying pathophysiological mechanisms of IBS have been considered and include concepts of gastrointestinal dysmotility, altered visceral sensitivity and perception, psychological distress, luminal irritants and post-infectious neuromodulation.[1,2,4-8] Overall, the brain-gut axis with elements of the central nervous system (CNS) and the enteric nervous system might contribute significantly to the pathogenesis of IBS. At present no specific, positive biological marker has been identified to confirm a diagnosis of IBS. On the basis of symptoms and the absence of structural, biochemical and physiological abnormalities a diagnosis of IBS can be made using the recently established Rome II criteria.[9]

Treatment of IBS is based on a trusted physician-patient relationship; it targets the predominant symptoms and might include psychological modalities.[1,2,4,6-13] The effectiveness of many drugs presently used in the treatment of IBS is questionable and often treatment remains unsatisfactory. Recently, however, a new class of drugs, the serotonin (5-HT) receptor modulating agents, has been introduced in the armamentarium and showed promising results in patients with IBS.[1-5,8,14-20]

In this article, we summarise the pharmacology, results of clinical trials and specific guidelines regarding the use of alosetron hydrochloride.[15-17,20] Alosetron is a 5-HT_3-receptor antagonist which was removed from the US market in November 2000, just months after it was initially approved, following reports of serious and life-threatening cases of ischaemic colitis and complications of constipation, including deaths. As a consequence of intense lobbying by individuals with IBS and IBS groups, the US FDA re-approved alosetron with tight restrictions on June 7, 2002.[21-24] It is now indicated only for women with severe diarrhoea-predominant IBS who have symptoms for at least 6 months and who have failed to respond to conventional therapy.[4,22,25] Post-marketing studies required by the FDA in conjunction with the reintroduction of alosetron will monitor physician prescribing behaviour and patient compliance.

1. Diagnosis and Treatment Irritable Bowel Syndrome (IBS)

Symptom-based criteria have been developed to facilitate the diagnosis of IBS since no structural, biochemical or physiological abnormalities or specific, diagnostic biological markers accompany the disorder.

These diagnostic criteria include the Manning criteria, and the Rome I and Rome II criteria.[9,10,12,13] The Rome II criteria, which are the most recently developed, define IBS by the presence of abdominal discomfort or pain -in the absence of structural or biochemical abnormalities- for at least 12 weeks, which need not to be consecutive, in the preceding 12 months. This pain or discomfort must be associated with at least two of the following three features: (i) pain is relieved with defaecation; (ii) the onset of pain is associated with a change in the frequency of bowel movements (diarrhoea or constipation); or (iii) the onset of pain is associated with a change in the appearance of the stool (loose, watery or pellet-like). Symptoms that cumulatively support the diagnosis of IBS include abnormal stool frequency (>3 bowel movements per day or <3 bowel movements per week), abnormal stool form (lumpy, hard or loose, watery), abnormal stool passage (straining, urgency or feeling of incomplete evacuation), passage of mucus, or bloating or the feeling of abdominal distension.

While the Rome I committee[12] had characterised subgroups of functional gastrointestinal disorders, including diarrhoea-predominant IBS and constipation-predominant IBS, the Rome II committee discouraged the use of IBS subtypes.[9,10] The American College of Gastroenterology Functional Gastrointestinal Disorder Task Force ('Task Force') agreed and recommended that patients with IBS should be identified using symptom-based criteria.[4,6]

A careful history can usually secure the diagnosis of IBS and distinguish it from organic diseases. Alarm symptoms indicating the presence of structural disease, include fever, anaemia, gastrointestinal blood loss, significant weight loss, family history of cancer, inflammatory bowel disease, caeliac disease, recent consistent changes in bowel habits, persistent, daily diarrhoea or constipation, and/or findings on physical examination should prompt routine diagnostic testing and appropriate management.[1-4,26]

In addition to using non-pharmacological approaches, such as diet and lifestyle changes, some patients with IBS benefit from drug therapy. Current treatment targets the predominant symptom of IBS for each individual patient.

A variety of medications, including tricyclic antidepressants and antispasmodics, have benefited selected patients with pain as the chief symptom.[2-4,18,26] However, they tend to increase constipation, particularly in IBS patients with constipation. Some direct smooth muscle relaxants also appear to be beneficial in alleviating IBS pain; however, most are not available in the US.[18] In patients with diarrhoea as the predominant symptom of IBS, loperamide reduces stool frequency and urgency. Cholestyramine is a second-line treatment for diarrhoea in IBS.[2,3] While bulking agents might alleviate constipation, anecdotal experience and laboratory data suggest that fibre products increased intestinal gas, bloating and abdominal discomfort in patients with IBS.[4] Alternatively, constipation might also be treated with osmotic laxatives, milk of magnesia, magnesium citrate or a polyethylene glycol solution.[2,3]

Pharmacological treatment of IBS remains unsatisfactory for a significant number of patients, due partly to the coexistence of several symptoms in an individual patient. Recently, new compounds have been developed that interact with the 5-HT receptors in the gut and, since they act on more than one symptom at a time, may represent an advancement in the treatment of IBS.[5,8]

2. Serotonin as Emerging Neuromodulator in IBS

The newest classes of drugs in the treatment of IBS are 5-HT-receptor agonists and antagonists. Serotonin is a major, monoamine-type neurotransmitter of significance in the enteric nervous system. Ninety-five percent of the serotonin in the body is found in the gut, mainly in the enterochromaffin-like (ECL) cells and in the enteric neurons;[8,19] the remainder is found in the CNS. Serotonin may enhance sensitivity of visceral neurons projecting between the gastrointestinal tract and the CNS,[5] and is involved in all integrated functions of the gut.

Serotonin is released from ECL cells in the gut, and exerts its diverse motor and sensory functions through submucosal and myenteric neurons via several serotonin receptors.[7] Serotonin activates secretory cells, and afferent and efferent neurons, and directly effects the gut smooth muscle leading to contraction and relaxation of the colonic wall.[5]

5-HT receptors are present on enteric neurons, ECL cells, gastrointestinal tract smooth muscle and, possibly, on enterocytes and immune cells. There are seven recognised 5-HT receptor families with multiple subtypes which have different actions in both the peripheral nervous system and the CNS.[5,7,8,19] Current knowledge of the 5-HT receptor family suggests the greatest relevance to the

treatment of IBS are the subtypes 5-HT_3 and 5-HT_4, which are found in the enteric nervous system, sensory ganglia, vagal afferents and brainstem. However, future work might elucidate other 5-HT receptor subtypes to be of clinical relevance in IBS as well.

The most promising agent interacting with the 5-HT_4 receptor is tegaserod.[8] Tegaserod is a partial 5-HT_4 receptor agonist and stimulates the peristaltic reflex, increases intestinal and colonic transit, reduces the firing rate of rectal afferent nerves and reduces visceral sensitivity.[4] The efficacy of tegaserod has been assessed in several randomised, controlled trials, and it has been approved for the short-term treatment of women with IBS whose primary bowel symptom is constipation.[4,27,28]

Both neurogenic contraction and relaxation has been induced *in vitro* by 5-HT_3 receptor activation in experimental animals. Stimulation of 5-HT_3 receptors leads to the release of substance P and acetylcholine, which are excitatory neurotransmitters for gastrointestinal tract smooth muscle. The observation that 5-HT_3 receptors are found in high concentrations in the enteric nervous system as well as in afferent neurons led to further studies evaluating the utility of 5-HT_3 receptor antagonists in IBS.[5,7,19,29,30]

Currently, the only commercially available 5-HT_3 receptor antagonist indicated for the treatment of IBS is alosetron. This agent slows colonic transit and decreases discomfort during distension of the colon.[2,4,22,29] Four clinical randomised, controlled trials[14-16,31] demonstrated statistically significant improvement in the primary study endpoints for alosetron-treated patients versus control patients. On this basis the 'Task Force'[4] stated that "Overall, the trials of alosetron consistently demonstrate high-quality study methodology and effectiveness for the treatment of IBS with diarrhoea in women".

3. Alosetron

Alosetron is a potent and highly selective 5-HT_3-receptor antagonist which has been evaluated for the management of IBS. It blocks the fast 5-HT_3-mediated depolarisation of guinea pig myenteric and submucosal neurons *in vitro* in a concentration-dependent manner. In clinical trials in patients with IBS, it increases the compliance of the colon to distension and delayed colonic transit.[5,19,29,30] A single dose of alosetron 4mg increased fluid absorption in a normal human small intestine.[29]

Alosetron does not accumulate in the plasma during repeated oral administration of 1mg twice daily. The oral bioavailability of alosetron is approximately 50% after a 4mg dose and approximately 60% after a 2mg dose in healthy volunteers. Alosetron is cleared by extensive metabolism by cytochrome P450 (CYP) enzymes CYP2C9, CYP3A4 and CYP1A2. It is mainly eliminated via the kidneys, mostly as 12 metabolites, with only 6% of the total dose recovered as non-metabolised drug. The plasma elimination half-life is approximately 1.5 hours for the parent compound and 3 hours for the parent compound plus circulating metabolites.[29,32]

Alosetron has been shown to decrease colonic transit and visceral sensitivity in patients with IBS. Alosetron 2mg twice daily for 8 days caused a decrease in left colonic transit.[33] In another study, alosetron 1mg twice daily resulted in a significant retardation of small bowel, and proximal and overall colonic, transit in patients with diarrhoea-predominant IBS with significantly greater responsiveness in females compared with males.[34] Similarly, alosetron 4mg twice daily for 7 days caused an increase in colonic compliance and a reduction in volume perception, but not pressure perception thresholds.[35] Alosetron may also act on 5-HT_3 receptors in the brain. In a study using positron emission tomography, alosetron 1mg twice daily was associated with reduced regional cerebral blood

flow of the central autonomic networks mediating emotional expression including the amygdala, ventral striatum and dorsal pons.[36]

3.1 Dose-Ranging Studies

The optimal dosage of alosetron was determined by two dose-ranging studies.[37,38]In one study, 462 non-constipated patients with IBS were randomised to alosetron 0.1, 0.5 or 2mg or placebo twice daily for 12 weeks.[37] Sixty-three percent of patients receiving alosetron 2mg compared with 51% of those receiving placebo reported improvement in abdominal pain/discomfort ($p < 0.05$). Smaller doses did not reach statistical significance in alleviating pain or discomfort. Patients receiving alosetron 2mg also had an increase in the number of pain-free days (41 vs 32 for placebo; $p < 0.05$) during the last 4 weeks of the study. At doses of 0.5mg and 2mg twice daily, alosetron significantly hardened stools and reduced stool frequency.

In the other dose-ranging study, 370 non-constipated patients with IBS were randomised to alosetron 1, 2, 4 or 8mg or placebo twice daily for 12 weeks. Most patients receiving alosetron 1 and 2mg twice daily reported adequate relief of their IBS symptoms compared with patients receiving placebo (60%, 59% and 33% for 1mg, 2mg and placebo, respectively; $p < 0.05$). With all dosages of alosetron, patients experienced improvement in stool consistency, frequency and percentage of days without urgency over placebo ($p < 0.05$) during the first month of the trial.[38]

3.2 Gender Differences

In the aforementioned trials,[37,38] the significant effects of alosetron were limited to females. However, due to the limited number of males enrolled, fewer than 40 per group in each study, definitive conclusions regarding the effectiveness of alosetron in males cannot be drawn from these studies.

Preliminary results of a study in 662 men with diarrhoea-predominant IBS found alosetron 1mg twice daily to have a statistically significant improvement in relief of IBS pain and discomfort compared with placebo. However, the effects of alosetron in men were not as robust as those seen in women.[39]

The reason for the greater effectiveness of alosetron in women than in men is unclear. The mechanism of action is independent of hormones and postmenopausal women respond as well as premenopausal women. Women appear to have a slightly greater systemic availability than men,[31] although this difference is unlikely to explain the clinical differences. The effects on alosetron on colonic transit are more pronounced in females than males, suggesting that the dose response in males may be different.[34]

3.3 Efficacy Studies

Because of the heightened effectiveness of alosetron in women, only women were enrolled in efficacy trials. Several large, multicentre, randomised, double-blind, placebo-controlled trials with alosetron 1mg twice daily were conducted. The primary endpoint in all but one of these trials was the patient's report of 'adequate relief' of pain or discomfort. Specifically, patients were asked the following question every 7 days: "In the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort?". A responder was defined as a patient who experienced adequate relief for at least 2 weeks in a month. Table I summarises the efficacy studies of alosetron in IBS.

In one of the trials,[15] 647 women with non-constipated IBS were randomised to alosetron 1mg or placebo twice daily for 12 weeks. Forty-one percent of women receiving alosetron, compared with 29% receiving placebo, reported 'adequate relief' for all 3 months of treatment. A greater percentage of women receiving alosetron than those receiv-

Table I. Efficacy trials with alosetron in irritable bowel syndrome (IBS)

Reference	Treatment	Patients (% female)	Study duration (wks)	Global outcome measure	Alosetron (% improved)	Placebo (% improved)
Camilleri et al.[15]	Alosetron 1mg bid vs placebo	647 (100)	12	Adequate relief of IBS pain and discomfort for at least 2 out of last 4 wks of the trial	56	47
Jones et al.[16]	Alosetron 1mg bid vs meberverine 135mg tid	623 (100)	12	Adequate relief of IBS pain and discomfort for at least 2 out of last 4 wks of the trial	58	48
Lembo et al.[17]	Alosetron 1mg bid vs placebo	801 (100)	12	IBS Global Improvement (moderate or substantial improvement in IBS symptoms over the previous 4 wks compared with the 3 mo prior to entry into the study)	76	44
Camilleri et al.[40]	Alosetron 1mg bid vs placebo	626 (100)	12	Adequate relief of IBS pain and discomfort for at least 2 out of 4 wks of each month	43	26

bid = twice daily; **tid** = 3 times daily.

ing placebo reported 'adequate relief' for each week of the study (figure 1). The effects of alosetron on 'adequate relief' of symptoms disappeared within 2 weeks of discontinuing the medication. The alosetron group also showed a decrease in stool frequency, a decrease in urgency and an increase in stool firmness[41] within 1 week of therapy commencement, although these effects were gone within 1 week of completing the study. Patients with diarrhoea predominant IBS had the largest treatment effect.

In another trial,[17] 801 women with non-constipated IBS and a lack of satisfactory control of bowel urgency (≥50% days) were randomised 2 : 1 to alosetron 1mg or placebo twice daily for 12 weeks. The primary endpoint of this trial was the proportion of days with satisfactory control of bowel urgency ("Have you had satisfactory control of your bowel urgency today: yes/no?"). A secondary endpoint was a new scale called the IBS Global Improvement Scale, which defined a responder as a patient who reported moderate or substantial improvement in IBS symptoms over the previous 4 weeks compared with the 3 months prior to entering the trial. Specifically, patients were asked monthly: "Compared to the way you usually felt during the 3 months before you entered the study, are your IBS symptoms over the past 4 weeks substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or substantially improved?". Patients treated with alosetron had a significantly greater number of days with satisfactory control of bowel urgency compared with placebo (73% vs 57%, $p < 0.001$). Similarly, alosetron improved bowel urgency in a greater percentage of patients within the first week of therapy and its effects lasted throughout the study. Furthermore, a significantly greater percentage of patients receiving alosetron

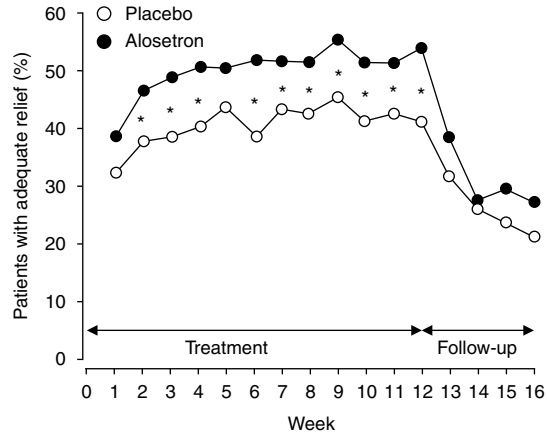

Fig. 1. The percentage of women with adequate relief of abdominal pain and discomfort from irritable bowel syndrome during the 12 weeks of treatment and 4 weeks of follow-up. * indicates $p < 0.05$ (reproduced from Camilleri et al.,[15] with permission from Elsevier).

were IBS Global Improvement responders compared with patients receiving placebo (76% vs 44%, $p < 0.001$).

In a third study,[16] alosetron was found to be significantly more effective than mebeverine, a smooth muscle relaxant commonly used in Europe but not available in the US. In this trial, 623 women with non-constipated IBS were randomised to receive alosetron 1mg twice daily or mebeverine 135mg three times daily for 12 weeks. Patients receiving alosetron experienced 'adequate relief' of pain and discomfort more frequently than did patients receiving mebeverine (58% vs 48%, respectively at week 12, $p < 0.001$), and there were significantly more responders to alosetron than to mebeverine during months 2 and 3 of treatment. Alosetron recipients had fewer days with urgency, and had decreased mean stool frequency and firmness of stool.

In a fourth study,[40] 626 non-constipated women were randomised to receive either alosetron 1mg or placebo twice daily for 3 months. Women with IBS receiving alosetron experienced 'adequate relief' of pain and discomfort at least 2 out of 4 weeks of each month more frequently than did patients receiving placebo (43% vs 26%, $p < 0.001$). Improvement with alosetron was observed by the end of the fourth week of the study and persisted throughout the study. Alosetron significantly decreased urgency and stool frequency, and caused firmer stools within 1 week of starting treatment.

On the basis of published clinical trials with alosetron the number of patients with diarrhoea predominant IBS needed to treat (NNT) to benefit one patient is approximately seven. This NNT is comparable with numbers reported for other drugs used in other chronic diseases.[42]

3.4 Pharmacogenetics

Polymorphisms in the serotonin reuptake process and the transporter protein (SERT) result in a decrease in protein expression and less reuptake of serotonin. The prevalence of SERT polymorphisms appears to be similar in patients with IBS to that in the general population and, therefore, it does not appear to play an aetiological role in IBS. However, SERT polymorphism may be important in determining patient response and possibly adverse reactions to alosetron as demonstrated in a study with 23 patients with diarrhoea-predominant IBS. In this study, patients who had long homozygous polymorphism had significantly greater slowing of colonic transit with alosetron than patients with heterozygous polymorphism.[11]

3.5 Health-Related Quality Of Life

In the trials discussed so far in this section, patients receiving alosetron showed improvement in health-related quality of life and work absenteeism. In addition, patients treated with alosetron had improved appetite, decreased dietary limitations and interference with social activities, and a greater ability to work and perform daily activities compared with patients receiving placebo.[43] The potential savings from increased productivity of a full-time employee treated with alosetron was estimated to be $US1013 per year (year of costs 1999).[44]

3.6 Adverse Effects

Constipation was the most common adverse effect reported in clinical trials, occurring in approximately 20–30% of patients receiving alosetron. While no dose-response relationship between constipation and the dose of alosetron was present (23%, 28%, 20% and 35% of female patients experienced constipation as an adverse event in the 1, 2, 4 and 8mg treatment groups, respectively), the higher dose (8mg) was associated with a higher rate of constipation than the lower doses of alosetron.[20] No serious complications were associated with constipation in the clinical trials, although patients in the clinical trials who did not experience a bowel

movement for 4 days were required to discontinue the study medication and had the option to use a laxative. Patients without a bowel movement for 7 days were withdrawn from the trial. However, post-marketing reports indicate that constipation associated with alosetron use may have been complicated by bowel obstruction, perforation, impaction and, possibly, toxic megacolon.

The mechanism of constipation from alosetron is probably the result of inhibition of excitatory motor pathways and reduction of intestinal fluids.

In clinical trials, four cases of suspected ischaemic colitis were reported; the incidence of ischaemic colitis was approximately 1 : 750. In each case the patient recovered without complications. In two of these cases, alternative causes for the colitis was possible. However, in subsequent reports no predisposing factors for ischaemic colitis, such as cardiovascular or peripheral vascular disease or hypercoagulability, were found.[45]

About 275 000 patients were taking the drug at the time of its withdrawal in November 2000. A post-marketing safety review found that up to March 8, 2002, there had been 84 reports of ischaemic colitis, with two deaths; 54 of these patients were hospitalised and 11 required surgery. Three deaths from small bowel ischaemia also appeared to be related to alosetron. In addition, there have been 113 reports of serious complications due to severe constipation, 83 resulted in hospitalisation, and 24 required surgery and two patients died.[22-24] On November 28, 2000, GlaxoSmithKline (GSK) met with the US FDA and other regulatory agencies, and the company withdrew alosetron voluntarily from the market.

4. Restrictions for the Use of Alosetron in the US

Following the withdrawal of alosetron from the market in November 2000, both the US FDA and GSK received thousands of comments from patients with IBS in whom the drug lessened their symptoms and improved the quality of their lives. As a consequence the FDA and GSK met to determine if a suitable risk management plan could be developed to allow the reintroduction of alosetron for those patients with 'severe' IBS. A supplemental new drug application was submitted by GSK and approved by the US FDA on June 7, 2002. Alosetron is not currently available outside the US. It is possible that the drug may become available outside the US in the future after an initial period of monitoring in the US.[25]

Alosetron is now indicated only for women with severe diarrhoea-predominant IBS who have symptoms for at least 6 months and who have failed to respond to conventional therapy. Severe IBS is defined in the labelling of alosetron as diarrhoea associated with frequent and severe abdominal pain, bowel urgency, faecal incontinence or restriction of daily activities. The FDA estimates that fewer than 5% of patients with IBS have severe disease as described and only a third of these have diarrhoea-predominant symptoms, which would make them eligible for alosetron treatment. The safety and effectiveness of alosetron in men and in patients under 18 years of age has not been established.

Alosetron is contraindicated in patients:

- with a history of chronic or severe constipation, or with a history of sequelae from constipation
- with a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation and/or adhesions
- with a history of ischaemic colitis, impaired intestinal circulation, thrombophlebitis or hypercoagulable state
- with current or a history of Crohn's disease or ulcerative colitis
- with active diverticulitis or a history of diverticulitis
- who are unable to understand or comply with the 'Patient-Physician Agreement'

- with known hypersensitivity to any component of the product.[46]

Physicians who plan to prescribe alosetron must participate in a prescribing programme, which requires the clinician to 'self attest' to their qualifications to diagnose and treat IBS, and recognise and manage complications of constipation and ischaemic colitis. Physicians must also agree to report serious adverse effects to the sponsor or to the FDA. To become a participant in the 'Prescribing Program' for alosetron, the clinician must contact GSK by telephone or on the Internet.[47] Information about the use of alosetron and its adverse effect profile need to be reviewed and a 'Physician Attestation Form' signed. Upon receipt of this form, the clinician will receive additional material needed to write prescriptions for alosetron. GSK provides the physician with stickers for alosetron that are affixed to the prescription. A medication guide is reviewed with the patient, and both the patient and the prescribing physician are required to sign a 'Patient-Physician Agreement Form', which becomes part of the medical record, prior to the initial prescription.

The current recommended starting dosage is 1 mg/day (half of the dosage used in clinical trials and recommended when the drug was first approved). Pharmacies will distribute bottles of 30 tablets to patients. If the patient shows no improvement after 4 weeks and the drug is well tolerated, the dosage of alosetron may be increased to 1mg twice daily. If there is no response to a dosage of 1mg twice daily for 4 weeks, the drug should be discontinued.

Pharmacies are required to only fill prescriptions (original and subsequent) with an attached sticker and not fill prescriptions transmitted by telephone, facsimile or computer generated prescriptions. A medication guide must accompany all prescriptions. Patients are asked to complete a follow-up survey to help to determine compliance with the 'Prescribing Program' for alosetron and to monitor adverse effects.

The FDA required a series of post-marketing studies to be performed by GSK as a contingency for the supplemental new drug application. These studies are described in the June 7, 2002 approval letter[25] and include the following.

- Conduct a randomised, double-blind, placebo-controlled study in women with severe diarrhoea-predominant IBS to determine the efficacy and safety of lower doses of alosetron.
- Conduct a randomised, double-blind, placebo-controlled study in women with severe diarrhoea-predominant IBS to determine the efficacy and safety of 'as needed' (prn) administration of alosetron at doses of 0.5mg once daily, 1mg once daily, 1mg twice daily and placebo.
- Obtain blood samples prospectively to allow DNA analysis to identify single nucleotide polymorphisms or haplotypes that predict adverse events in patients who develop ischaemic colitis and determine genotype of polymorphic CYP enzymes (1A2 and 2C9) responsible for alosetron metabolism.
- Propose and conduct mechanistic studies to investigate the pathophysiological aetiology of alosetron-induced ischaemic colitis and small bowel ischaemia.
- Perform studies to determine drug interactions with fluvoxamine and ketoconazole as well as pharmacokinetic studies in hepatically impaired individuals.
- Perform a large epidemiological study on the safety and use of alosetron in US practice.

The company has no plans for the use of patient samples nor will it conduct a direct-to-consumer marketing programme.

The 'Task Force'[4] established the effectiveness of alosetron for IBS with diarrhoea in women and further stated: "Physicians should follow the FDA-approved indications for alosetron: women with severe, diarrhoea-predominant IBS who have failed to respond to conventional therapy. Therefore, given

the risk of serious adverse events with alosetron, physician and patient judgement will guide selection of patients who are appropriate candidates for alosetron. Physicians should educate patients about the potential risk of alosetron and instruct patients to discontinue alosetron if constipation occurs".

The 'Task Force' findings notwithstanding, the FDA was criticised by opponents of re-approval who argued that severe adverse effects and deaths occurred even without preceding warning signals, and that the drug, therefore, poses a serious and significant public health concern.[23,24,48-50]

5. Conclusions

IBS is a common gastrointestinal disorder that is associated with significant adverse health effects. Current medical therapy in a significant number of patients remains inadequate. The reintroduction of alosetron by the FDA attempts to balance the potentially serious adverse effects of this drug with the need for more effective therapy in women with severe diarrhoea-predominant IBS unresponsive to conventional therapy. It remains to be established whether the plan agreed upon by the FDA and GSK will adequately educate physicians to appropriately identify patients most likely to benefit from this drug and limit the sequelae of constipation and ischaemic colitis.

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