Cilansetron: a novel, high-affinity 5-HT_3 receptor antagonist for irritable bowel syndrome with diarrhea predominance

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Irritable bowel syndrome (IBS) is associated with significant morbidity, impaired quality of life, work absenteeism and high healthcare costs. Current drug treatments, with the exception of drugs targeting serotonin receptor subtypes, are of limited value. Tegaserod (Zelnorm™, Novartis Pharmaceuticals Corp., NJ, USA), a partial agonist, is useful in women with the constipation-predominant form of IBS. Alosetron (Lotronex™, GlaxoSmithKline plc, London, UK), a 5-HT_3 receptor antagonist, is effective in women with severe diarrhea-predominant IBS; however, its use is limited and it is restricted to the USA. Cilansetron is a potent and selective 5-HT_3 receptor antagonist that is being developed for IBS with diarrhea predominance (IBS-D). It delays colonic transit and reduces visceral hypersensitivity. In large, randomized controlled trials, cilansetron has been shown to improve global and specific IBS-D symptoms, including abdominal pain/discomfort, stool frequency, stool consistency, urgency and health-related quality of life in men and women. Cilansetron is well-tolerated, with constipation being the most frequent adverse event. Treatment with cilansetron, similar to that with alosetron, is associated with a low incidence of suspected ischemic colitis events. Alosetron was withdrawn temporarily from the US market, and indefinitely from the European market because of severe complications of ischemic colitis. To date, the few suspected ischemic colitis events associated with cilansetron have resolved within 30 days of drug discontinuation, without any complications. Epidemiologic studies indicate that patients with IBS have a greater risk of ischemic colitis, irrespective of treatment; this underscores the need for additional research on the natural history of IBS and potential treatment-related adverse events.

Keywords: 5-HT_3, cilansetron, clinical studies, diarrhea, intestinal motility, irritable bowel syndrome, ischemic colitis, quality of life, treatment, visceral hypersensitivity

Irritable bowel syndrome (IBS) is a common chronic and relapsing gastrointestinal (GI) disorder characterized by abdominal discomfort or pain, bloating and abnormal bowel habits [1]. Its prevalence varies between 11.5 and 15% in the Western world. Only one in five individuals with IBS seeks medical advice. The syndrome affects all age groups, with a clear female predominance [2–4].

Patients with IBS have a significantly poorer health-related quality of life than both the general population and patients with chronic organic GI disorders. IBS-related symptoms may impair social and occupational functioning and are among the most frequent causes of work absenteeism [1,5–7]. Direct and indirect IBS-related medical costs are considerable, and patients with IBS impose greater costs to the healthcare services than matched patients without this condition [8].

The pattern of symptoms of IBS varies considerably between individuals. IBS with diarrhea predominance (IBS-D), one of the subtypes of this condition, represents approximately a third of cases [9,10]. The subtype is associated with accelerated small bowel and colonic transit [11,12]. Common symptoms of IBS-D include abdominal pain or discomfort, frequent loose stools and urgency. While most patients experience mild-to-moderate symptoms, some experience symptoms that are severe and persistent enough to warrant pharmacologic therapy [1].

IBS-D is a complex disorder that is associated with abnormal GI motility, and altered intestinal secretion and visceral hypersensitivity; the underlying mechanisms are not well understood. However, the past 20 years have seen a revolution in the understanding of the enteric nervous system, GI motor and sensory functions and neuroenteric pharmacotherapy. GI motor, secretory and sensory functions are known to be regulated by a variety of neurotransmitters, including serotonin (5-hydroxytryptamine [5-HT]). Serotonin appears to play a key role in modulating GI functions through a number of 5-HT receptor subtypes, especially the 5-HT_1, 5-HT_3, and 5-HT_4 receptor subtypes. Altered 5-HT signalling may disturb

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intestinal motor activity and sensation, resulting in diarrhea or constipation and increased perception of visceral stimulation [13–17].

Recent progress in the field of pharmacotherapy has enabled the development of drugs targeting specific serotonergic receptor subtypes. These agents typically provide relief from multiple symptoms of either IBS with constipation predominance (IBS-C) or IBS-D [18–22]. Tegaserod, a selective and partial 5-HT_4 receptor agonist that increases the peristaltic reflex and decreases visceral sensitivity, was shown to provide global relief of IBS-C symptoms in clinical trials [18,19]. It appears to be a promising option for use in patients with severe IBS-C who do not respond to standard therapy [23]. Alosetron, a selective, 5-HT_3 antagonist that impedes intestinal transit and prolongs colonic transit time was the first drug to demonstrate global symptom efficacy in nonconstipated IBS patients. Alosetron provided adequate relief of abdominal pain and discomfort, and improved bowel symptoms when compared with placebo; however, these beneficial effects were seen exclusively among women [20,21]. Constipation was one of the most frequently reported adverse events with alosetron. Due to several reported cases of alosetron-associated serious ischemic colitis, and resultant complications, the use of the drug has been restricted to a select group of patients [22,24] and is currently only available in the USA. Tegaserod is available in the USA, Switzerland and a few countries outside Europe.

Cilansetron, a potent and specific 5-HT_3 receptor antagonist, has been developed for the treatment of IBS-D in men and women. This review provides an overview of cilansetron, including its structure, pharmacodynamic profile, results of preclinical study data, safety profile, tolerability and clinical applications.

Overview of the irritable bowel syndrome with diarrhea predominance market: currently available drugs

In recent years, there has been an increasing demand for IBS-D treatments that are reliable, effective and offer multiple symptom relief. No single drug is effective in treating all of the intestinal and nonintestinal symptoms of IBS. Loperamide (Imodium®, Ortho–McNeil Pharmaceutical, Inc., NJ, USA), an opioid agonist that slows colonic transit, proved superior to placebo in relief of diarrhea and urgency, but failed to relieve IBS-associated pain [25,26]. It may even aggravate abdominal pain and distension and cause constipation. Low-dose tricyclic antidepressants (TCAs) have been used for severe abdominal pain and their anticholinergic properties may have a beneficial effect on diarrhea [27,28]. However, TCAs are not approved for the treatment of IBS and their use in IBS is limited because of their adverse event profile. Antispasmodics have been used effectively for relief of IBS-D-associated abdominal pain; however, their efficacy in treating symptoms of diarrhea is limited.

Alosetron was the first 5-HT_3 antagonist approved for use in women with IBS-D and effective dosages of 1 to 2 mg twice daily were shown to provide adequate relief of global IBS symptoms and improved health-related quality of life (QoL) [29]. Alosetron was withdrawn from the market following several cases of serious ischemic colitis, severe constipation and death. Lack of effective treatment options for IBS-D and pressure from patient advocacy groups led to the reapproval of alosetron in the USA; however, its use is now restricted to women with severe refractory IBS-D. Physicians also are required to enroll in the Lotronex Prescribing Program in order to ensure that the drug is prescribed only by qualified physicians to the appropriate patient population [30,31].

Introduction to cilansetron

Chemistry

On the basis of the structures of ondansetron (Zofran®, GlaxoSmithKline plc, London, UK) and GR 65,630, ring-opened C-linked methylimidazole analogs, novel 1,7 anneleated indole derivatives, including cilansetron, were synthesized as potential 5-HT_3 antagonists [32]. Annelation resulted in compounds being several times more potent than ondansetron and GR 65,630. The chemical name of cilansetron is 10-R(-)-5,6,9,10-tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl)methyl]-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-1 monohydrochloride monohydrate.

Pharmacology

Cilansetron has a high affinity for the 5-HT_3 receptor and has been shown to be more potent than ondansetron both *in vitro* and *in vivo* [32,33]. van Wijngaarden and colleagues showed that competitive antagonism achieved at the 5-HT_3 receptors *in vitro* is ten-times greater than that of ondansetron [32]. In the von Bezold–Jarisch reflex test in unrestrained conscious rats, cilansetron is orally active at a dose six-times lower than that of ondansetron.

In mice, the lowest effective dose affecting behavioral parameters is ten-times higher for cilansetron than for ondansetron [32]. These studies indicate that cilansetron is a potent and selective 5-HT_3 antagonist.

Pharmacokinetics & metabolism

Cilansetron is extensively metabolized by the liver. The two main 4-OH metabolites of cilansetron, the 4S- and 4R-hydroxymetabolites, also act as 5-HT_3 receptor antagonists *in vitro* and might contribute to the biologic effects of cilansetron, but to a lesser degree than the parent compound [34].

The effect of hepatic impairment on the pharmacokinetics of cilansetron (repeated oral 8 mg doses) and its metabolites was assessed by Pardue and colleagues in an open-label, parallel-group study [35]. There was a 26% decrease in apparent clearance and a twofold prolonged half-life in subjects with hepatic impairment, compared with healthy subjects. Further pharmacokinetic studies indicated that female patients tended to have a decreased clearance of an oral dose of cilansetron [36].

Animal studies

The potential benefit of cilansetron on visceral pain has been described in animals. Cilansetron potently inhibited or reduced distension or chemically induced visceral sensitivity in animal models [37–39]. In addition, cilansetron antagonized serotonin induced responses of mesenteric afferent nerve terminals [14].

In the rat jejunum, the dose of cilansetron applied intraluminally resulted in a greater degree of antagonism on the serotonin response than intravenous administration, indicating that cilansetron is active at its site of absorption [14].

In preclinical studies, cilansetron also had an effect on GI motility. Cilansetron prevented the delay in gastric emptying after intraduodenal administration of lipids in dogs [39]. This study indicated that this effect may be mediated via mucosal sensory afferent nerves, also suggesting that 5-HT_3 ligands, such as cilansetron, may act locally on afferent nerve terminals following absorption across the mucosa.

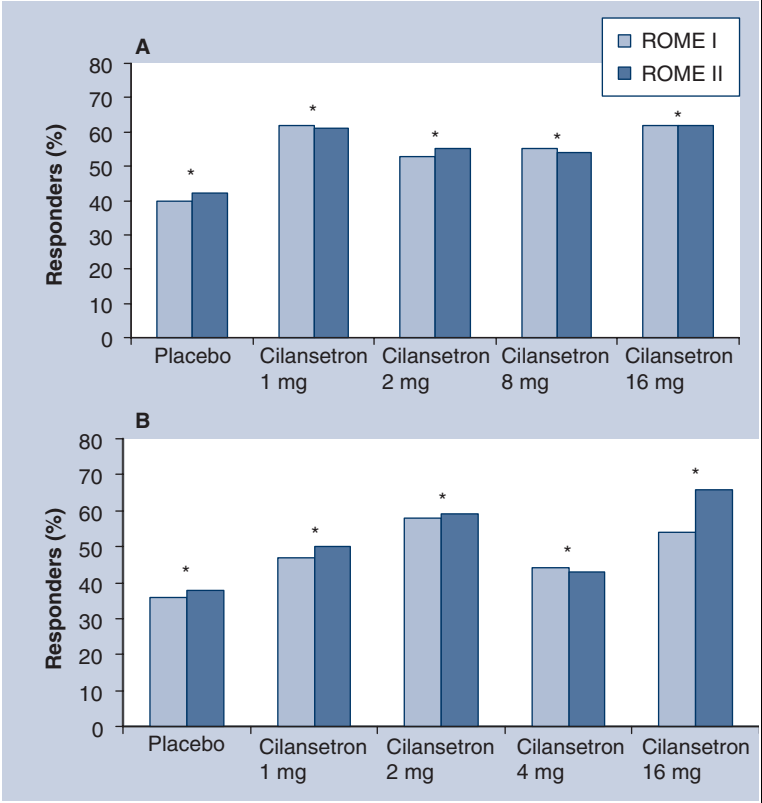
Clinical efficacy

Phase II studies

Phase II trials in healthy volunteers examined the effects of cilansetron on colonic transit and visceral perception. Oral cilansetron 8 mg given three-times daily had clear effects on colonic motility and perception of visceral distension. It increased phasic contractile activity in the sigmoid colon in healthy volunteers, which is likely to impede transit, and improved stool consistency [40,41]. Cilansetron also had a consistent moderate dose-dependent inhibitory effect on total colonic transit [41,42].

There is also evidence that cilansetron can alter the perception of visceral stimuli in healthy subjects. Cilansetron 8 mg three-times daily increased the distension thresholds of gastric visceral perception and tended to increase the esophageal pain threshold [43,44]. The mechanism underlying the effect of cilansetron on visceral perception is not known. Patients taking the cilansetron 2 mg three-times daily dose showed the largest improvement in adequate relief of IBS symptoms (abdominal pain/discomfort and abnormal bowel habits) as assessed by patient response over the 1, 4 mg, and 16 mg three-times daily doses. The results have been reported in abstract form. Caras and colleagues reported response rates from two dose-finding, 12-week trials in men and women with IBS-D (defined by the ROME criteria) [45,46]. Response was defined as adequate relief of global IBS symptoms for at least 50% of weekly responses. One of these studies was a placebo-controlled, randomized, multicenter US study enrolling 471 patients. Response rates for adequate relief of IBS symptoms (primary efficacy parameter) for the intent-to-treat (ITT) population ($n = 454$) were 40% for placebo, 62% for cilansetron 1 mg ($p < 0.01$), 53% for 2 mg (nonsignificant), 55% for 8 mg (nonsignificant) and 62% for 16 mg ($p < 0.01$) three-times daily. Overall response rates were similar for men and women at all doses, except the 1-mg dose which showed a higher rate in women. In the second multinational study, response rates for adequate relief ranged from 47% (1 mg three-times daily) to 59% (2 mg three-times daily). No differences in efficacy parameters were seen when IBS patients were characterized using the ROME I versus the more stringent ROME II criteria (**Figure 1**). In the US study, abdominal pain scores improved for the 2 mg three-times daily and 16 mg three-times daily doses only. Cilansetron decreased stool frequency and consistency in a dose-dependent fashion up to the 8 mg three-times daily dose. The 1 mg three-times daily dose provided adequate relief of IBS symptoms and improved stool consistency.

Figure 1. Comparison of the response rates for adequate relief of global irritable bowel syndrome symptoms in nonconstipated patients defined according to ROME I or ROME II criteria [46].



(A) US study; **(B)** Canada/Europe study.
*Not significant.
US Study: ROME I (n = 471), ROME II (n = 438).
Canada/Europe study: Rome 1 (n = 435), ROME II (n = 389).

Phase II studies in IBS-D patients showed promising results with significantly higher response rates with cilansetron compared with placebo – in both men and women.

Phase III studies

The efficacy and safety of cilansetron 2 mg three-times daily for the treatment of IBS-D was evaluated in three Phase III studies published in abstract form. Subset analyses based on data from two Phase III trials have been performed to assess the benefits of cilansetron in men. Results reported from a 6-month double-blind, placebo-controlled, multinational study in IBS-D patients indicated that cilansetron effectively relieved global IBS symptoms [47]. The primary efficacy parameter was the proportion of subjects in the two study groups who reported adequate relief of IBS symptoms in 50% or more of the responses to the weekly questions on abdominal pain/discomfort and abnormal bowel habits. The ITT population consisted of 792 patients meeting the ROME criteria for IBS-D (358 men and 434 women). With respect to abdominal pain/discomfort, a greater proportion of the cilansetron-treated group reported relief when compared with placebo (61 vs. 46%; $p < 0.001$). The proportion of patients in the cilansetron study arm reporting relief of abnormal bowel habits was also greater than in the placebo group (63 vs. 46%; $p < 0.001$). Females and males responded equally well to cilansetron (**Table 1**). Cilansetron treatment was generally well-tolerated; 9% of the patients treated with cilansetron and 7% treated with placebo withdrew from the study because of an adverse event.

Miner and colleagues reported the results of a 3-month, double-blind, placebo-controlled, multicenter trial of cilansetron 2 mg three-times daily, conducted in the USA with 487 women and 205 men meeting the ROME criteria for IBS-D [48]. Response rates (≥50% positive responses for weekly adequate relief) for overall IBS symptoms were 49% for cilansetron as compared with 28% for placebo ($p < 0.001$) resulting in an absolute benefit increase (ABI) of 21% ($p < 0.0001$). The percentages of patients reporting adequate relief of abdominal pain/discomfort taking cilansetron and placebo were 52% and 37%, respectively ($p < 0.001$) and relief of abnormal bowel habits were reported by 51% and 26%, respectively ($p < 0.001$). Similar response rates were reported for men and women (41% vs. 52%).

Table 1. Proportion of male and female irritable bowel syndrome with diarrhea predominance patients reporting relief of irritable bowel syndrome with cilansetron 2 mg three-times daily, compared with placebo over a 6-month period [47–49].

	Abdominal pain/discomfort			Abdominal bowel habits		
	Cilansetron	*Placebo*	*p-value*	*Cilansetron*	*Placebo*	*p-value*
Males	57%	45%	0.02	60%	44%	0.002
Females	64%	46%	<0.001	67%	48%	<0.001

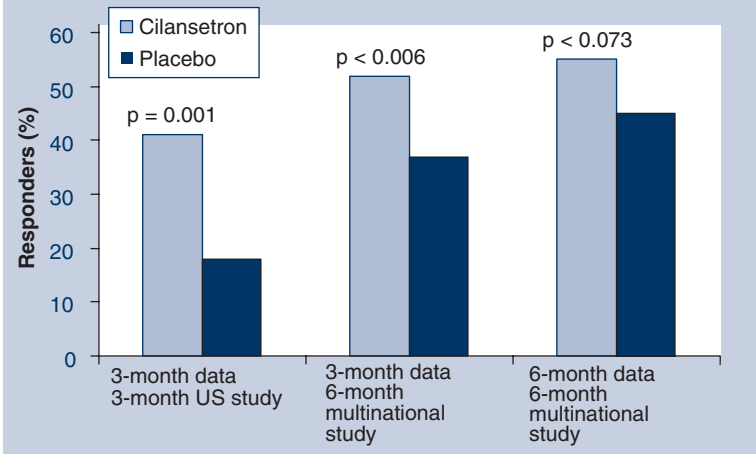
Males (n = 358) ; Females (n = 434)

A subset analysis conducted in two of the Phase III trials, (a 3-month US study with 205 men [48] and a 6-month multinational study with 358 men in the ITT population [47] demonstrated that cilansetron was effective in men for the relief of IBS symptoms [49]. In the 3-month US study, results favoring cilansetron over placebo for overall IBS symptoms as well as for individual symptoms of abdominal pain/discomfort and abnormal bowel habits, including diarrhea and urgency, were statistically significant in men. Similar results also were observed in the 6-month multinational study (**Figure 2** & **Table 2**).

In another subset analysis of the Phase III trials, Clouse and colleagues demonstrated that cilansetron significantly improved specific IBS symptoms such as stool frequency, stool consistency and urgency in patients with IBS-D [50].

Phase III trials demonstrated that cilansetron provided adequate relief of global IBS symptoms and also had a positive effect on health-related quality of life. A subanalysis by Olden and colleagues used data from the 6-month multinational trial on 338 patients who completed the IBS-QoL questionnaire at baseline and after 6 months of treatment. Cilansetron 2 mg three-times daily increased the IBS-QoL composite score by 17.7, compared with 9.6 for placebo ($p < 0.001$), indicating a significant improvement in QoL with cilansetron treatment [51].

Figure 2. Overall responder rate for relief of irritable bowel syndrome with diarrhea predominace symptoms for male subjects [49].



*Not significant.
US Study (n = 205).
Canada/Europe Study (n = 358).

Safety & tolerability

In the US dose-finding study of cilansetron, dose-dependent constipation and flatulence were observed at higher frequencies with cilansetron compared with placebo. No cases of ischemic colitis were reported [45]. In the 6-month multinational study, side effects leading to study withdrawal occurred in 9% of subjects with cilansetron and 7% with placebo. Constipation was the most frequently reported side effect. Three suspected ischemic colitis events were observed in the cilansetron group and all resolved without sequelae upon treatment discontinuation; no cases were reported in the placebo group [47]. In the 3-month study, 12% of patients in the cilansetron 2 mg three times daily group and 6% in the placebo group withdrew from the study. Constipation was reported for 19% of patients in the cilansetron group and 4% in the placebo group. Headache was more common in the cilansetron than in the placebo group (6 vs. 3%). One patient with suspected ischemic colitis recovered without sequelae after 7 days [48].

Subanalyses of data from Phase III US and multinational studies demonstrated constipation with cilansetron treatment in 8 and 7% of male patients with IBS-D, respectively, and in less than 1% of male patients with IBS-D receiving placebo, irrespective of the data pool. No cases of ischemic colitis were identified in either subanalysis [49]. Laboratory abnormalities of clinical significance were not reported in healthy volunteers or patients with IBS-D receiving cilansetron therapy.

Conclusions

Cilansetron is a potent, and highly selective 5-HT_3 antagonist; like other compounds of this class, it has an effect on intestinal motility and transit, as well as on visceral sensitivity. In healthy volunteers and in patients with IBS-D, cilansetron delays colonic transit in a dose-dependent manner. In animal studies, cilansetron potently inhibited or reduced visceral hypersensitivity and the responses to nociceptive stimuli in the colon, through mechanisms that have yet to be elucidated. In healthy volunteers, cilansetron also tended to increase the threshold of visceral perception. In various large, placebo-controlled trials, cilansetron treatment produced sustained improvement of global IBS-D symptoms as well as individual symptoms of abdominal pain/discomfort, stool frequency, consistency and urgency. In contrast to alosetron, cilansetron

Table 2. Overall responder rate for relief of abdominal pain or discomfort and relief of abnormal bowel habits for males for the 3-month US study and the 6-month multinational study [49].

Parameters	Cilansetron 2-mg three-times daily (%)	Placebo (%)	E (%)	p-value*
Abdominal pain or discomfort				
US study‡ 3-month	45	23	22	0.001
Multinational study§ 3-month	52	39	13	0.012
6-month	57	45	12	0.021
Abnormal bowel habits				
US study‡ 3-month	39	17	22	<0.001
Multinational study§ 3-month	60	35	25	<0.001
6 month	60	44	16	<0.002

**General Estimation Equation Analysis; ‡US Study (n = 205); §Multinational Study (n = 358).*

is equally effective in men and women. Besides IBS-D symptom reduction, cilansetron has also been shown to improve health-related QoL. Head-to-head studies comparing the efficacy and safety of cilansetron and alosetron have not been conducted to date.

Cilansetron appears to have a favourable adverse event profile. The most common adverse event is dose-dependent constipation. Unlike alosetron, serious life-threatening complications from constipation have not been observed with cilansetron when used at the recommended dose of 2 mg three-times daily. The suspected ischemic colitis events observed with cilansetron were transient and all patients recovered upon treatment discontinuation without any complications. It also is important to note that in patients with IBS, the development of ischemic colitis may be a manifestation of the natural history of the IBS itself [52,53].

Based on the available data, it is appropriate to conclude that cilansetron is a viable treatment option for men and women with IBS-D, an invalidating condition for which no other treatment that improves global symptoms and Qol currently is available.

Expert opinion

Before the introduction of alosetron, there were few large scale clinical trials supporting the routine use of pharmacological agents in patients with IBS-D [54]. Although it is generally believed that most patients with IBS do not require pharmacological therapy, some patients have symptoms that are severe enough to impact their Qol, contributing to factors such as work absenteeism and lost productivity. In such patients, the use of drugs targeting specific symptoms of IBS may be warranted [55,56]. TCAs have traditionally been used to treat abdominal pain in patients with debilitating symptoms [28] and loperamide has been useful in relieving symptoms of diarrhea and urgency [25]. However, neither antidepressants nor opioids have been studied extensively in large-scale, randomized, controlled trials of the syndrome. Antispasmodics have been used to treat the symptoms of abdominal pain associated with IBS-D and are approved for this indication in many countries; they are not effective in relief of the bowel symptoms associated with IBS-D.

Alosetron was the first pharmacologic agent to demonstrate improvements in IBS-D-associated abdominal pain and diarrhea, and also resulted in improvements in health-related QoL [22]; however, the drug is only indicated for use in women; its efficacy has not been demonstrated in male patients. Furthermore, the risk of developing ischemic colitis with potentially fatal complications precludes an unrestricted use of alosetron in women with IBS-D [57].

From the clinical studies reviewed so far, it seems that the benefits of cilansetron may outweigh those of alosetron. Although cilansetron and alosetron have not been compared directly in clinical trials, both agents are effective in relieving global IBS symptoms, including abdominal pain/discomfort and diarrhea. However, only cilansetron is effective in relieving these symptoms in both men and women with IBS-D [49]. Cilansetron also appears to have a more favourable adverse-event profile compared with alosetron. With the implementation of an appropriate risk-management program,

cilansetron can be an effective and reliable treatment option for men and women with IBS-D.

Five-year view

Emerging science indicates that serotonin plays a significant role in regulating GI motility, and potentially, pain perception. The latest therapeutic options for IBS, including the 5-HT_3 antagonists and 5-HT_4 agonists all provide symptomatic relief through their interactions with 5-HT receptors. Of these agents, cilansetron is the first 5-HT_3 antagonist that provides relief of abdominal pain and bowel symptoms in both men and women with IBS-D. It offers an alternative to conventional therapy, particularly for patients that may not show an adequate response to available treatment options. Although the risk of ischemic colitis and potential complications appears to be low with cilansetron; the agent's safety will only be firmly established with long-term use. In light of alosetron's marketing history and evidence suggesting that patients with IBS are three- to four-times more likely to develop ischemic colitis than the general population [58,59], it is imperative to educate patients and physicians on the benefit-to-risk ratio of cilansetron, as well as appropriate drug use and adverse event management. A realistic risk management program may pave the way for more widespread use of cilansetron in the near future.

Key issues

- At present, there is an unmet need for irritable bowl syndrome with diarrhea predominance (IBS-D) treatment options that offers adequate symptom relief combined with an acceptable adverse-event profile.
- Pharmacologic therapy is warranted for patients whose IBS-D symptoms are severe enough to interrupt daily activities and negatively impact quality of life.
- Cilansetron is a novel 5-HT_3 antagonist that has been shown to improve multiple IBS-D symptoms, including abdominal pain, stool frequency and urgency, as well as health-related quality of life.
- The efficacy of cilansetron has been demonstrated in male and female patients with IBS-D.
- In clinical trials of cilansetron, the most commonly observed adverse event was constipation. A few suspected ischemic colitis events have also been observed; these have resolved upon drug discontinuation without further sequelae.
- With physician awareness and proper patient selection, cilansetron is likely to be a promising treatment option for patients with IBS-D.

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