Valentina Noemi Madia¹, Antonella Messore¹, Francesco Saccoliti¹, Valeria Tudino¹, Alessandro De Leo¹, Daniela De Vita², Martina Bortolami¹, Luigi Scipione¹, Ivano Pindinello¹, Roberta Costi¹,* and Roberto Di Santo¹

¹Dipartimento di Chimica e Tecnologie del Farmaco, Istituto Pasteur - Fondazione Cenci Bolognetti, “Sapienza” Università di Roma, p.le Aldo Moro 5, I-00185 Rome, Italy; ²Dipartimento di Biologia Ambientale, “Sapienza” Università di Roma, p.le Aldo Moro 5, I-00185 Rome, Italy

Abstract: Background: Tegaserod (Zelnorm®) is a 5-hydroxytryptamine (serotonin) type 4 receptor agonist for the treatment of hypomotility disorders of the lower gastrointestinal tract associated with the irritable bowel syndrome with constipation (IBS-C).

Objective: The authors provide the reader with a better understanding on tegaserod mechanism of action, on its pharmacodynamics and pharmacokinetic properties, on safety and tolerability, with a summary of the key published clinical trials conducted in patients with irritable bowel syndrome (IBS). Its effects on colon inflammation have also been described.

Results: Tegaserod was withdrawn in 2007 due to increased risks of cardiovascular adverse effects. The manufacturer denied this, because pre-existing cardiovascular disease or risk factors were attributed to all affected patients. Thus, no causal relationship between tegaserod use and cardiovascular events was clearly shown. A matched case-control study of tegaserod-treated with untreated patients found no association between tegaserod and adverse cardiovascular outcomes. Despite its adverse effects, tegaserod resulted to be effective in treating chronic constipation in adult women aged < 65 years with IBS-C, while the safety and effectiveness of tegaserod in men with IBS-C have not been established.

Conclusion: Tegaserod was resubmitted to the Food and Drug Administration in 2018 for use in a low-risk population. Moreover, tegaserod has also been shown to improve symptoms, enhance gastric accommodation and significantly attenuate visceral pain arising from the colon in functional dyspepsia patients. Treatment with tegaserod seems also to exert a protective effect in inflamed colons, reducing the severity of colitis in animal models.

Keywords: 5-HT₄ agonist, abdominal pain, chronic bowel disorder, clinical trials, constipation, irritable bowel syndrome, tegaserod maleate, Zelnorm®.

1. INTRODUCTION

Irritable bowel syndrome (IBS) is a common condition of the digestive system: a functional disorder characterized by altered bowel habits discomfort and self-evident abdominal pain, with a prevalence of around 10-15% in populations of developed countries and with a female predominance [1-4]. About 15% of adults and 9-10% of children are affected by IBS, and one-third of them manifest irritable bowel syndrome with constipation (IBS-C) as a predominant symptom. It can also cause stomach cramps, bloating and diarrhoea [5, 6].
The lack of any biomarker [5, 7] makes the diagnosis of IBS difficult and the study of its causes turns out to be challenging. Although it is hypothesized from in vivo studies that this syndrome is related to an increased sensitivity of the entire gut [8], its exact cause remains unknown [9]. To date, IBS is not correlated to a single fully plausible organic cause and several theories describe it as a multifactorial disease [10, 11]. Due to the high morbidity, IBS represents an economic and humanistic burden of illness [12, 13].

Current guidelines recommend not only a pharmacological therapy, in order to control specific symptoms, but also nonpharmacological measures such as psychological counseling, lifestyle changes, regular physical activity, and nutritional therapy [14].

With the aim to avoid the underlying hypomotility associated with slow-transit constipation and ineffective oesophageal motility, many therapeutic agents have been designed to stimulate muscle activity [15]. Nowadays, the existence of a communication route between the gastrointestinal tract (GI) and the brain (gut-brain axis) and that neuronal signaling affect this connection is well known [16].

The neurotransmitter serotonin, 5-hydroxytryptamine (5-HT) plays an important role in the pathogenesis of subsets of patients with IBS. It is known that approximately 95% of the body’s 5-HT is synthesized in the enterochromaffin, mast and smooth muscle cells of the GI tract. 5-HT, acting through the intrinsic nervous system of the GI tract, is believed to play a critical role in GI motor, sensory and secretory functions [17]. To date, seven families of 5-HT receptors have been identified (5-HT1−5-HT7). These receptors, found in the central and peripheral nervous system, are G protein-coupled except for the 5-HT3 receptor, a ligand-gated ion channel, which activate an intracellular second messenger cascade to produce an excitatory or inhibitory response. Moreover, 5-HT receptors classes can be categorized in 14 subtypes, and of these, 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT3, 5-HT4 and 5-HT7 receptors are distributed in the enteric nervous system or smooth muscle in the gut. 5-HT1A, 5-HT1B receptors inhibit neurotransmitter release while 5-HT3 and 5-HT4 receptors are the excitatory subtypes. Activation of 5-HT1A receptors inhibits the release of acetylcholine and the contraction of smooth muscle. Indeed, 5-HT1A receptor agonists enhanced gastric accommodation in patients with functional dyspepsia in clinical studies and increase lower oesophageal sphincter tone and slow gastric emptying in human [18]. Sumatriptan, a selective 5-HT1B receptor agonist, induces a lag phage for gastric emptying of liquids and increases the amplitude and duration of esophageal contractions in humans. 5-HT2B (that are expressed by the smooth muscle of the adult human gut, mediating excitatory effects in human colon and contributing to the putative 5-HT-induced colonic smooth muscle hypersensitivity associated with IBS) [19].

5-HT1p, 5-HT3 and 5-HT4 receptors are the most clinically relevant in GI tract functioning. Indeed, activation of 5-HT1p (expressed on intrinsic primary afferent neurons in the submucosa), 5-HT3 (expressed throughout the central and peripheral nervous systems) or 5-HT4 (Gs-coupled inducing an increase of the cellular levels of c-AMP and located in the alimentary tract, urinary bladder, heart and adrenal gland as well as the central nervous system) receptors enhances GI transit. Additionally, intrinsic afferents, utilizing 5-HT3 receptors, may be involved in a reflex circuit within the gut that increases motility and intestinal secretions. 5-HT3 and 5-HT4 receptors are expressed by the mucosal terminals of the intrinsic sensory neurons and mucosal application of serotonin activates local reflex pathways via 5-HT3 receptors and enhances peristalsis via the same receptors. Additionally, accumulating evidence suggests a potential role for the 5-HT7 receptor subtype in GI motor function. This receptor sets off a cascade of events starting with the release of the stimulatory G protein Gs from the GPCR complex that in turn activates adenylylate cyclase which increases intracellular levels of c-AMP. The 5-HT7 receptor plays a role in smooth muscle relaxation within the vasculature and in the gastrointestinal tract. Moreover, it is present in the central nervous system and it is involved in thermoregulation, circadian rhythm, learning and memory, mood regulation and sleep [20].
The stimulation of GI propulsive motility should be improved with the release of acetylcholine from motor neurons promoted by the activation of 5-HT₄ receptor (5-HT₄R) on cholinergic nerve endings in the enteric nervous system [21, 22]. Based on these pharmacological observations, 5-HT₄R agonists, including tegaserod, were developed for the treatment of hypomotility disorders [23].

Tegaserod is a non-selective 5-HT ligand, associated with 5-HT₄R partial agonist and 5-HT₂B receptor antagonist properties [24]. Novartis developed it for the treatment of hypomotility disorders of the lower GI tract associated with IBS [25, 26]. Its activity is based on the stimulation of the GI motility and the improvement of the peristaltic reflex, with subsequent reduction of abdominal pain [27].

After its withdrawal in 2007 due to concerns about cardiovascular effects, it was resubmitted to the Food and Drug Administration (FDA) in 2018 for use in a restricted population [28].

Tegaserod standard dosage is 6 mg twice a day (BID). It accelerates gut transit by increasing the peristaltic reflex and facilitating fluid secretion into the colonic lumen. Tegaserod is effective in treating adult women aged < 65 years with IBS-C [29-33].

Tegaserod is an indole carbazimidamide derivative of 5-HT (Fig. 1). Compared with 5-HT, tegaserod has a guanidine moiety rather than a protonated amine in the indole side chain [34, 35]. Due to its physicochemical properties, tegaserod exerts prokinetic effects in the lumen directly because it is poorly absorbed and is largely excreted unmetabolized in stool [36]. Indeed, tegaserod has a bioavailability of only 10% and approximately two-thirds of tegaserod is excreted unchanged in faeces, so most of the drug is available to act locally on enterochromaffin cells and locally high concentrations of the drug might, therefore, be reached to inhibit SERT, which might add to its prokinetic action [37].

Interestingly, tegaserod also demonstrated to be effective in attenuating dyspeptic symptoms and significantly reduce abdominal pain in functional dyspepsia (FD) patients [38, 39].

This review provides the reader with a better understanding on tegaserod mechanism of action, on its pharmacodynamics and pharmacokinetic properties, on safety and tolerability, with a summary of the key published clinical trials conducted in patients with IBS. Its effects on colon inflammation have also been described.

2. ROLE OF 5-HT IN IBS

5-HT produces effects through various neurocrine, paracrine and endocrine pathways; it is directly involved in initiating the peristaltic reflex, in facilitating intraluminal secretions, and strongly implicated in the pathophysiology of IBS [42].

Many GI tract processes are regulated by 5-HT through the 5-HT₄Rs and are involved in triggering peristaltic reflex, modulating smooth muscle tone and intestinal secretion, as demonstrated by in vitro studies using human GI tissue specimens [43].

Moreover, in the GI tract, 5-HT contributes to vasodilation, and sensation, [44] and it also has both neuroprotective [45] and pro-inflammatory actions in the gut [46]. Indeed, the 5-HT₄R is located on enteric nerve terminals where it mediates...
presynaptic facilitation of neurotransmitter release when activated. 5-HT₄ receptors are also highly expressed in the colonic epithelium, where they appear to be expressed by all epithelial cells [47]. Epithelial 5-HT₄Rs mediate a variety of responses, including 5-HT release, chloride secretion and goblet cell degranulation, as well as enhanced propulsive motility and reduced visceral hypersensitivity [40].

Thus, 5-HT₄ agonists and/or antagonists may be useful in normalizing motor and sensory dysfunction that occur in patients with IBS [42, 48].

2.1. Pharmacological Treatment of IBS-C

Traditionally, pharmacologic therapy for IBS-C has been directed at relieving specific symptoms, typically those that are the most frequent, severe or life-altering for the patient. The initial approach involves dietary modifications, such as avoidance of foods known to exacerbate symptoms and foods capable of producing excess gas. Addition of dietary fiber may be beneficial, although it may worsen symptoms of bloating. Osmotic laxatives, such as lactulose or magnesium salt, can be helpful in IBS-C. Abdominal pain and discomfort are usually treated with antispasmodic agents, such as dicyclomine and hyoscyamine. These agents are anticholinergic and block depolarization of intestinal smooth muscle. Antispasmodic agents may be useful for the treatment of abdominal cramping and bloating, but no solid evidence confirms their efficacy in IBS-C. Antidepressants, both tricyclics and selective serotonin reuptake inhibitors, may have a role in diarrhea-predominant IBS but do not improve IBS-C. Even so, such pharmacologic therapies are largely unsatisfactory and only modestly effective in the treatment of IBS-C, mainly due to the multifaceted and poorly understood pathophysiology of this disorder. Furthermore, side effects are not uncommon with these agents, limiting their usefulness in clinical practice [26, 49, 50].

Yet, despite the well-recognized need for more efficacious and safer treatments, few novel treatment compounds have been approved for clinical use. The need for a drug therapy that effectively treats all of the symptoms of IBS-C, improves the patient’s health-related quality of life, and can be used safely on a chronic basis remains unfulfilled.

Recently approved drugs and novel investigational compounds are expected to streamline the management of IBS-C. The main classes of drugs that have been the subject of active research in recent years are prokinetics, prosecretory agents or secretagogues, and bile acid modulators (Fig. 2) [26, 49, 50].

Enhancement of contractile force, coordination of intestinal contractions, and augmentation of intestinal secretions can facilitate the movement of bowel contents through the GI tract. Although their performance in clinical trials has been inconsistent, drugs with prokinetic activity in the GI tract may help to normalize gut neuromuscular function and play an important role in the treatment of functional bowel disorders, such as the IBS. Several 5-HT receptor ligands have either been approved or are in clinical development for the treatment of IBS. Some compounds have demonstrated increased specificity for individual 5-HT receptors over others. Drugs belonging to this group are benzamides and derivatives as, for example, cisapride, renzapride, mosapride and prucalopride [50].

Cisapride is a benzamide derivative that has mixed pharmacologic actions on 5-HT receptors. It both antagonizes the 5-HT₃ receptor and agonizes the 5-HT₄ receptor. Cisapride’s prokinetic mechanism of action is thought to result from the facilitation of ACh release at the myenteric plexus [51]. Cisapride was shown to accelerate gastric emptying and intestinal transit, but to have limited effects on altering bowel function [52]. Some studies demonstrated efficacy for cisapride in the treatment of chronic constipation [53]. However, the data regarding the clinical efficacy of cisapride in C-IBS patients have been inconsistent [54]. The availability of cisapride is currently limited commercially due to its association with cardiac dysrhythmias and patient deaths [55]. For organic synthesis, see literature [56].

Another substituted benzamide compound, renzapride, with similarities to cisapride, demonstrates both 5-HT₃ and 5-HT₄ receptor activity and has been reported to possess prokinetic activities. Renzapride’s promotility actions are thought to be due to its stimulating actions via the 5-HT₄ receptor agonist activity and subsequent facilitation of
cholinergic neuronal function. The pharmacologic properties of this compound may prove beneficial for the treatment of IBS; however, published clinical data are not available to support this assertion. In an early controlled trial in patients with IBS and constipation, the drug demonstrated acceptable global improvements over placebo for both men and women. In contrast to cisapride, renzapride has not been reported to be associated with cardiac side effects [20]. For organic synthesis, see literature [57].

Clebopride was designed to increase the antidopaminergic activity (against D2 receptors), and it also acts on the upper GI [58]. For organic synthesis, see literature [59].

Mosapride is a gastrokinetic having 5-HT4 receptor agonism, 5-HT3 receptor antagonism but not D2 antagonism. While cisapride was suspended from the market, mosapride has not been limited due to the risk of arrhythmias, but it might not be safe because the metabolisms of both cisapride and mosapride are inhibited by CYP3A4 inhibitors [58]. For organic synthesis, see literature [60].

Prucalopride represents a new chemical class of benzofurans. It is a selective agonist at 5-HT4 receptors and has been shown to enhance colonic motility. Studies have demonstrated a lack of measurable affinity for muscarinic type 3 (M3) receptors, 5-HT2A and 5-HT3 receptors, and cholinesterases. The relatively long half-life, rapid Cmax, and rapid plasma uptake provide an excellent pharmacokinetic profile. Prucalopride has been shown to enhance GI transit in patients with functional constipation compared to placebo [61]. No published data are available regarding the efficacy of prucalopride in patients with IBS, but IBS patients have been included in clinical studies. The
current state of development of this compound is unclear following early concerns over carcinogenicity in animal studies, and possible cardiac effects [20]. For organic synthesis, see literature [62].

Velusetrag is dihydroquinoline-carboxylic acid derivative. It is a highly selective 5-HT₄ receptor agonist having no effect on hERG channel. Velusetrag has one major metabolite being a 5-HT₄ receptor agonist as potent as the parent drug, and the AUC ratio of the metabolite to velusetrag is approximately 0.5 in human administered with 15 mg of velusetrag. The compound has the elimination half-life of about 16 and 35 hours after single and multiple dosing, respectively [20]. For organic synthesis, see literature [63].

Moreover, in the last decade, intestinal secretion has been the subject of active research for the development of treatments for CC and IBS-C. The chemical and clinical characteristics of prosecretory agents, drugs that augment intestinal secretion, thus acting as a stool lubricant and facilitating its evacuation [50]. Examples are lubiprostone, linaclotide e plecanatide. Lubiprostone, a chloride channel activator, was the first secretagogue to be investigated and approved for the treatment of CC and IBS-C. Chloride channels have been recognized as the major effectors of fluid transport and secretion in the intestinal lumen. In particular, type-2 chloride channels (CIC-2) have been explored with regard to their role in CC and IBS-C. Lubiprostone is a highly specific activator of CIC-2 channels that lead to increased intestinal secretion, an effect that requires the cystic fibrosis transmembrane, conductance regulator. A phase 2 double-blind RCT demonstrated that lubiprostone reduced abdominal pain in IBS-C patients, though higher doses were associated with more adverse events, namely nausea and diarrhea. Lubiprostone was approved by the United States FDA in April 2006 for the treatment of CC in men and women, and in April 2008 for the treatment of IBS-C in women [50]. For organic synthesis, see literature [64].

Linaclotide, a minimally absorbed first-in-class peptide agonist of guanylate cyclase C (GC-C), was recently approved for the treatment of IBS-C and CC. GC-C mediates intestinal secretion in response to heat-stable enterotoxins, the major cause of Escherichia coli-induced secretory diarrhea. Linaclotide binds to GC-C, which is richly present on the luminal surface of the intestinal enterocytes, and ultimately activates CFTR, resulting in the secretion of chloride and bicarbonate into the intestinal lumen. Consequently, intestinal fluid secretion is increased, stools are softened, and colonic transit may be accelerated. The dual action of linaclotide on both constipation and abdominal pain in IBS-C is likely related to its approval by both the United States FDA and the EMA [50]. For organic synthesis, see literature [65].

Similar to linaclotide, plecanatide is a minimally absorbed GC-C agonist believed to act on both intestinal secretion and nociception. Preliminary results from a phase II RCT that is underway in patients with IBS-C have suggested that plecanatide is effective, well-tolerated, and safe at doses up to 9 mg [50]. For organic synthesis, see literature [66].

Bile acid modulators have been used to treat constipation disorders based on the observation of increased incidence of diarrhea in patients taking bile acids for gallstones or cholestatic liver diseases, and in patients with terminal ileum disease or resection. The enhancement of colonic secretion and motility is caused mainly by the deconjugation of bile acids in the colon to secondary bile acids. Thus far, two drugs, sodium chenodeoxycholic acid (CDC) and elobixibat, have been investigated for the treatment of IBS-C and CC. CDC is a primary biliary acid that has been in use for many years for the dissolution of gallstones. In clinical studies, the main adverse event of CDC was dose-dependent diarrhea that is of the secretory type, due mainly to intracellular activation of adenylate cyclase and increased intestinal permeability. In phase III double-blind RCT of 36 women with IBS-C, CDC (500 or 1000 mg, once daily) increased stool frequency, softened stools and improved straining, with lower abdominal cramping as the most commonly reported adverse event. Therefore, CDC has the potential to be used as a “physiologic laxative” for the treatment of IBS-C [50].

Elobixibat is a first-in-class ileal bile acid transporter inhibitor that is currently being investi-
gated for the treatment of CC. Elobixibat has some potential advantages over currently approved drugs (prucalopride, lubiprostone, linaclotide). First, given its negligible systemic absorption, it is unlikely to induce cardiovascular toxicity, a theoretical effect of prucalopride. Second, it has a positive effect on both secretion and motility of the colon, while lubiprostone and linaclotide are only secretagogues, without any direct effect on colonic motility. Two-phase II RCTs focusing on the efficacy of elobixibat in CC demonstrated significant improvement of all constipation parameters while the efficacy of elobixibat for the treatment of IBS-C has not yet been investigated [50]. For organic synthesis, see literature [67].

Notably, the search for safer and more effective drugs for the treatment of IBS-C is ongoing, with clinical trials underway to evaluate various pharmacologic options, including drugs already approved for other gastrointestinal indications as for antibiotics neomycin and rifaximin [50].

2.2. Comparison with the Safety of Other Drugs

Traditionally, pharmacologic therapy for IBS-C has been directed at relieving specific symptoms, typically those that are the most frequent, severe or life-altering for the patient [68]. The initial approach involves dietary modifications, such as avoidance of foods known to exacerbate symptoms and foods capable of producing excess gas [69]. Addition of dietary fiber may be beneficial, although it may worsen symptoms of bloating. Osmotic laxatives, such as lactulose or magnesium salt, can be helpful in IBS-C. Abdominal pain and discomfort are usually treated with antispasmodic agents, such as dicyclomine and hyoscyamine. These agents are anticholinergic and block depolarization of intestinal smooth muscle. Antispasmodic agents may be useful for the treatment of abdominal cramping and bloating, but no solid evidence confirms their efficacy in IBS-C [70]. Antidepressants, both tricyclics and selective serotonin reuptake inhibitors, may have a role in diarrhea-predominant IBS but do not improve IBS-C [71]. Even so, such pharmacologic therapies are largely unsatisfactory and only modestly effective in the treatment of IBS-C, mainly due to the multifaceted and poorly understood pathophysiology of this disorder. Furthermore, side effects are not uncommon with these agents, limiting their usefulness in clinical practice [26, 49, 50].

Yet, despite the well-recognized need for more efficacious and safer treatments, few novel treatment compounds have been approved for clinical use. The need for a drug therapy that effectively treats all of the symptoms of IBS-C, improves the patient’s health-related quality of life, and can be used safely on a chronic basis remains unfulfilled.

Recently approved drugs and novel investigational compounds are expected to streamline the management of IBS-C. The main classes of drugs that have been the subject of active research in recent years are prokinetics, prosecretory agents or secretagogues, and bile acid modulators [26, 49, 50].

Table 1 [50] provides a concise summary of the abovementioned drugs used for the management of IBS-C, irrespective if they are available or not on the market or still in the development phase including a brief mention on their mechanism of action, and the most frequent adverse events and safety issues as determined in relevant clinical trials that have investigated these treatment options.

3. ACTIVITY OF TEGASEROD

3.1. Mechanism of Action on 5-HT₄R

Tegaserod (for the organic synthesis see literature [87]) is structurally similar to 5-HT and was synthesized as a partial agonist to mimic the actions of endogenous 5-HT (Fig. 3) on gastrointestinal 5-HT₄Rs [88]. The drug lacks additional blocking activities of the 5-HT₃ and dopamine D₂ receptors [89]. These last two receptors are associated with constipation [90] and central adverse effects [91], respectively. Besides intestinal secretion [92], tegaserod modulates normal and altered motility throughout the GI tract [93-95] and inhibits visceral afferent responses upon colorectal distension [96, 97]. Cisapride and renzapride have 3- to 8-fold lower affinity for 5-HT₄R compared to that of tegaserod (pKD 7.7, expressed as molar (M) unit) [98]. Tegaserod shows a 4-fold higher affinity for human 5-HT₄Rs than 5-HT (pKD 7.1 expressed as molar (M) unit) [98]. Although the presence of peripheral 5-HT₄Rs [43] in human atrial tissue [99], it was
### Table 1. Comparison of tolerability and safety of drugs used in the pharmacological management of IBS-C and CC.

| Drug          | Target Receptor/Affinity                                                                 | Activity                                      | Frequent AEs, Safety Issues                        | Approval/Development Status                                                                 |
|---------------|-----------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------|
| **1. Prokinetic Agents** |                                                                                       |                                               |                                                  |                                                                                              |
| Cisapride [72, 73] | Nonselective 5-HT₄ agonist and 5-HT₃ antagonist                                          | Local Ach release, ↑ GI transit               | Diarrhea, Abdominal pain, ↑QTc interval, Fatal arrhythmias | Approval 1993, Withdrawal 2000                                                              |
| Renzapride [74, 75] | Full 5-HT₄ agonist and 5-HT₃/5-HT₂b antagonist                                           | Local Ach release, ↑ GI transit               | Diarrhea, Abdominal pain, Headache, Flatulence, No ↑QTc interval | Phase III RTCs terminated due to poor efficacy                                              |
| Clebopride, [76] | Full 5-HT₄ agonist                                                                      | ↑ peristaltic reflex, ↑ Intestinal secretion | Diarrhea, Abdominal pain, Headache, Flatulence, ↑risk of serious CV events |                                                                                              |
| Mosapride [76]  | Partial agonist                                                                         | ↑ Colonic transit (HV/CC)                     | Diarrhea, Nausea, Abdominal pain, Headache        | US Approval 2002 for IBS-C, US Approval 2004 for CC, US and Other Countries withdrawal in 2007, US Emergency use only in 2009, India withdrawal in 2011, No EU Approval US remarket 2018 for use in restricted population |
| **Tegaserod [29, 33, 77, 78]** | 5-HT₄ and 5-HT₁ partial agonist                                                         | ↑ Colonic transit (HV)                        | Diarrhea, Nausea, Abdominal pain, Headache        | EU Approval 2009 and Canada 2011 for CC                                                     |
| **Prucalopride [79]** | High selectivity/affinity for 5-HT₄                                                   | ↑ Colonic transit (HV/CC)                     | Diarrhea, Nausea, Abdominal pain, Headache        |                                                                                              |
| **Naronapride [79]** | Full 5-HT₄ agonist (GI-tr) Partial agonist (heart)                                      | ↑ Colonic transit (HV)                        | Diarrhea, Headache                               | Phase II RTCs completed in CC                                                               |
| **Velusetrag [79]** | Potent, selective 5-HT₄ agonist/high affinity                                          | Dose dependent↑ Colonic transit (HV)          | Diarrhea, Nausea, Vomiting, Headache              | Phase II RTCs completed in CC                                                               |
| **Rose-010 [79]** | GLP-1 analogue                                                                          | ↑ Colonic transit, Antinociceptive effect in IBS-C | Nausea, Headache                               | Phase II RTCs completed in IBS-C                                                            |
| **Itopride [80]** | Dopamine D₂ antagonist and AChE Inhibitor                                               | Gastrokinetic, ↑ Intestinal transit           | Diarrhea, Headache                               | Phase II RTCs completed in IBS-C in the US Registered in Japan and other Far East Countries in other indications |

(Table 1) contd…
| Drug | Target Receptor/Affinity | Activity | Frequent AEs, Safety Issues | Approval/Development Status |
|------|--------------------------|----------|-----------------------------|----------------------------|
| 2. Prosecretory Agents | | | | |
| Lubiprostone [81] | Activation of CIC-2 by direct action on epithelial cells provoking intestinal fluid secretion | ↑ Ileum and Colonic transit | Diarrhea, Nausea, Abdominal pain | US Approval 2008 for IBS-C in women and CC in adults and 2013 for OIC, UK Approval 2012 for CC and 2014 for OIC |
| | | | | |
| Linaclotide [82] | Binding to GC-C with stimulation of cGMP and CFTR-mediated secretion | Dose dependent ↑ Colonic transit | Diarrhea dose dependent | US Approval 2012 for IBS-C and CC, EU Approval 2012 for IBS-C |
| | | | | |
| Plecanatide [83] | GC-C receptor activation with CFTR-mediated secretion | Probable ↑ Colonic transit | Diarrhea dose independent, Nausea | Phase II RTCs completed, Phase III in CC ongoing, Phase II in IBS-C ongoing |
| 3. Bile Acid Modulators | | | | |
| Sodium chenodeoxycholic acid [84] | De-conjugation to secondary bile acids | ↑ Colonic transit | Diarrhea, Nausea, Abdominal cramping/pain | Phase III RTCs completed in IBS-C |
| | | | | |
| Elobixibat [85] | IBAT inhibitor | Dose dependent ↑ Colonic transit | Diarrhea, Abdominal cramping/pain | Phase II RTCs completed in CC, RTCs for extended safety ongoing |
| 4. Drugs Registered in other Indications | | | | |
| Neomycin/Rifaximin [86] | Neomycin: protein synthesis inhibitor Rifaximin: Bacterial RNA synthesis inhibitor | Eradication of methane, ↑ Intestinal transit | Neomycin: Neuro-, Oto-, Nephro-toxicity Rifaximin: Headache, Nausea, Dizziness, Fatigue | Phase II RTCs completed in IBS-C |

AEs=Adverse Events; Ach=acetylcholine; ↑=Increase/acceleration; ↓=Decrease; CV=Cardiovascular; RTCs=Randomized Clinical Trials; IBS-C=Irritable Bowel Syndrome Constipation predominant; CC=Chronic Constipation; US=United States of America; EU=European Union; GI-tr=Gastrointestinal tract; GLP-1=Glucagon-like peptide-1; HV=Healthy Volunteers; CIC-2=Chloride channel-2; GC-C=Guanylate cyclase-C; cGMP=Cyclic Guanosine Monophosphate; CFTR=Cystic Fibrosis Transmembrane conductance Regulator; OIC=opioid-induced constipation; IBAT=Ileal Bile Acid Transporter; AChE=Acetylcholinesterase.

postulated that cardiovascular adverse effects (AE) observed with these compounds are not 5-HT₄ receptor-related. Indeed, 5-HT₄ receptor agonists are able to express tissue selectivity, i.e. behave as a partial agonist in some and as a full agonist in other tissues. Furthermore, the concept of ligand-directed signalling offers great opportunities for future drug development by enlarging the scientific basis for the generation of agonist-specific effects in different cell types, tissues or organs [35].

3.2. Effects of Tegaserod on Colonic Inflammation

5-HT can exert a pro-inflammatory effect in the GI tract [100]. For instance, colitis is reduced in mice lacking or deficient in mucosal 5-HT [101], and it is worsened in SERT knockout mice, which have elevated mucosal 5-HT availability [102]. This effect is likely mediated by activation of 5-HT₇ receptors on dendritic cells in the lamina propria [46].
Tegaserod administration exerts epithelial 5-HT₄R stimulation that reduces disease activity and histological damage in both dextran sodium sulfate (DSS) and trinitrobenzene sulfonic acid (TNBS) colitis, supporting an anti-inflammatory effect. The epithelial 5-HT₄R stimulation can exert its protective effects through several mechanisms, including increased epithelial proliferation, enhanced epithelial cell migration, and resistance to oxidative stress-induced apoptosis. Furthermore, treatment with the 5-HT₄ agonist attenuated inflammation-induced changes in colonic motor function. Importantly, all of these effects were blocked by the 5-HT₄ antagonist, GR113808, and protection was not detected in 5-HT₄ knockout mice [40]. Furthermore, epithelial 5-HT₄Rs serve an important physiological role in maintaining mucosal integrity since inhibition of 5-HT₄R activity in normal animals leads to inflammation and disrupted motor function, providing evidence for an anti-inflammatory role of 5-HT₄ in normal physiology. In addition to these protective, anti-inflammatory actions of epithelial 5-HT₄Rs, there is evidence that 5-HT₄Rs play a beneficial, neurogenic effect in the muscularis as the administration of tegaserod improves the rate of propulsive motility of TNBS-inflamed guinea pigs. As in the TNBS inflamed guinea pig colon, mice with DSS colitis exhibited a slowing of colonic transit that was inhibited by tegaserod treatment. Furthermore, the effect of tegaserod was blocked by the 5-HT₄ antagonist, GR113808 [40].

One mechanism by which tegaserod is acting is through enhanced wound healing processes since an increase both in cell proliferation and in epithelial cell migration in a 5-HT₄ antagonist-sensitive manner was observed. Epithelial erosions, ulcers and decreased epithelial barrier integrity are all common features of active colitis, and these condi-
tions would likely be mitigated by enhanced epithelial proliferation and migration [40]. Indeed, treatment with tegaserod significantly accelerated the recovery from DSS colitis as compared to vehicle-treated animals [40]. These effects were blocked by the 5-HT4 antagonist. Moreover, in established TNBS colitis, tegaserod accelerated recovery of the disease activity index and this action was also inhibited by antagonist treatment [40].

The anti-inflammatory effects of 5-HT4R activation may also involve resistance of the epithelium to the harmful effects of oxidative stress. Oxidative stress, and resultant epithelial apoptosis is a key feature of inflammation and has been demonstrated in both DSS and TNBS colitis [101]. Treatment with tegaserod protected CaCo-2 cells from apoptosis that was elicited by the free radical donor, H2O2, in a 5-HT4 antagonist-sensitive manner. Treatment with tegaserod in two different models of colitis decreased the extent of inflammation as it was occurring, and accelerated the process of remission once colitis had been established. The discovery that 5-HT4Rs also contribute to the epithelial integrity in healthy animals reveals a newly identified role for 5-HT signaling in the mucosal layer [40].

Interestingly, tegaserod proved to attenuate the visceral sensitivity by reducing the Fos protein, substance P (SP) and calcitonin gene-related peptide (CGRP) expression in the lumbarsacral spinal cord induced by colon inflammation in rats [41]. Fos, one of the inducible transcription factors, serves as a quantifiable marker to identify neuronal populations activated by noxious stimulations. Noxious stimulation of hollow viscera induced a specific pattern of Fos expression in rat spinal cord that reflected the intensity of the stimulation [103]. Neurons in the dorsal horn of lumbar-sacral spinal cord are activated via sensory afferent fibers in the pelvic nerve by noxious stimulation induced by persistent colonic inflammation. Therefore, tegaserod can dose-dependently prevent these sensory neurons from being activated by colonic inflammation [41].

SP was released from primary sensory nociceptive neurons in response to noxious stimuli. SP could play a pivotal role at the spinal cord level in postsynaptic sensitization, particularly during and after gut inflammation [104]. The density of SP in the dorsal horn decreased significantly compared to the control group after treatment with tegaserod. Therefore, tegaserod can inhibit SP expression in the dorsal horn of the spinal cord, exerting antinociceptive effect [41].

CGRP is one of the major neuropeptides expressed in the spinal cord sensory processing region and is widely distributed in the nervous system. CGRP is likely to be involved in pain transmission and may produce a direct nociceptive effect. CGRP might also enhance SP-induced nociceptive sensation by facilitating the release of SP in the spinal dorsal horn [105]. Compared with that of the control group, the density of CGRP decreased in treatment groups, suggesting that tegaserod may not act on CGRP expression to reduce visceral nociceptive transmission. However, whether a much larger dose of tegaserod can significantly decrease CGRP expression in the spinal cord still needs more studies [41].

3.3. Efficacy of Tegaserod in the Treatment of Functional Dyspepsia

FD is defined as the presence of one or more of four gastroduodenal symptoms including epigastric pain, epigastric burning, postprandial fullness, and early satiety, in the absence of organic disease [106, 107]. Although the etiology and pathophysiology of FD are not well understood, recent studies have suggested that abnormalities in GI motility, abnormal sensorimotor function (hypersensitivity to distention and impaired meal accommodation), genetic factors, psychosocial factors, and Helicobacter pylori infection may be implicated in the pathophysiology of FD [108].

In a randomized controlled trial (RCT) [111], the efficacy of tegaserod in the treatment of FD was evaluated. It showed a significantly higher
response rates and improvement of symptoms in patients treated with tegaserod compared to the placebo group [38].

4. TEGASEROD AND IBS-C

4.1. Preclinical and Clinical Pharmacokinetics (PK)

Tegaserod PK and metabolism were investigated in animals and in vitro using human liver and intestinal slices, as well as rat and human liver microsomes.

After oral administration in rats and dogs, the drug was absorbed by approximately 30% and 60%, respectively and exhibited an extensive first-pass metabolism in both species. The terminal elimination half-life ($t_{1/2}$) was 2 hours in rats and 7 hours in dogs. The major metabolite in both species, 5-methoxy-indole-3-carboxylic acid glucuronide M29.0 (Scheme 1), showed no pharmacologic activity [112]. Nevertheless, there is a potential for tegaserod and M29.0 to increase platelet aggregation in vitro. In one in vitro study, tegaserod, at concentrations up to 10-times the maximum plasma concentration ($C_{max}$) at the recommended dose, significantly increased platelet aggregation in a concentration-dependent manner up to 74% compared to vehicle control. In another in vitro study, M29.0 also showed a 5% to 16% increase in platelet aggregation compared to vehicle control. The clinical implications of the in vitro platelet aggregation results are unclear [32].

Most discussions of tegaserod’s activity have been limited to the activity of intact tegaserod and inactivity of its major metabolite M29.0. Completely absent from these discussions, as from the Figure, is the fate in humans of half of the molecule, the pentyliaminoguanidine (PAG) also generated when tegaserod undergoes acid hydrolysis in

---

**Scheme 1.** Pre-systemic and systemic metabolism of tegaserod.
the stomach. The 2018 FDA Briefing Document simply states the following: “Information on systemic absorption of PAG in humans is not available” [28]. One mole of PAG is generated for every mole of M29.0 and of M7.0. Blood levels of both metabolites are substantial: $C_{\text{max}}$ for M29.0 is 16-fold and M7.0 8-fold higher than tegaserod’s. Hence PAG’s blood levels could be 24-fold higher than tegaserod’s. Regardless, PAG could exert effects in the gut instead of or in addition to those in the blood.

PAG could have direct impacts upon both the efficacy and safety of tegaserod. PAG is a derivative of guanidine that has a labeled adverse effect of diarrhea, as well as increased peristalsis, that may preclude use [113]. Hence tegaserod’s modest benefits could be related to PAG rather than intact tegaserod.

There are several PAG safety concerns. For instance, guanidine has a labeled warning regarding fatal bone marrow suppression [113]. A low neutrophil count is an adverse event listed in the tegaserod label [114]. Moreover, tegaserod produces small intestine mucosal hyperplasia and adenocarcinoma in mice. Despite blaming this finding on PAG, the developer estimated a safety margin for human exposure based on tegaserod dosages alone [28]. All in vitro receptor, drug interaction, and genotoxicity studies omitted PAG entirely [113].

Information is also lacking on the metabolites enclosed in square brackets in Scheme 1. Like PAG, they may have appreciable blood levels and they may be pharmacologically active since one of them is 5-methoxyindole-3-carboxylic acid, a positional isomer of 5-methoxyindole-2-carboxylic acid, that is a potent hypoglycemic agent [115].

Tegaserod clinical PK was investigated after single and multiple oral (tablet or capsule) or i.v. administration, in healthy volunteers, special populations and patients with IBS, all groups containing both male and female individuals. The range of investigated doses was 2 mg - 12 mg BID.

The absolute bioavailability of tegaserod was approximately 10% (Table 2). Variability in the area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) and maximum drug concentration ($C_{\text{max}}$) following oral administration was greater than the i.v. one. The variability in the absorption of tegaserod and the limited oral availability were associated with a first-pass effect and the acceleration of GI transit [116, 117]. After single oral administration in fasting conditions (12 mg), tegaserod was rapidly absorbed. Maximum plasma concentration ($C_{\text{max}}$) of about 5.5 ng/mL was achieved in 1.5 hours ($t_{\text{max}}$) and the mean exposure ($AUC_{0-\infty}$) was 17.1 ng*h/mL. Administration under fed conditions reduced both the rate ($C_{\text{max}}$) and extent ($AUC_{0-\infty}$) of absorption of tegaserod by 20-40% and 40-65%, respectively (Table 2). Moreover, the lag time and $t_{\text{max}}$ were increased [116-119]. The terminal half-life following oral or i.v. administration was about 11 hours [96, 116, 117]. The reduced absorption of tegaserod under fed circumstances was attributed to decreased solubility associated with a rising gastric pH [117, 118].

Following single and repeated oral administration of 2 to 100 mg (BID, for 5-14 days), tegaserod showed linear (dose and time-independent) PK. After 5 days of treatment at the recommended dose (6 mg BID), steady-state was already achieved. No relevant accumulation was observed (Table 3) [116, 117, 120, 121].

High plasma protein binding, mainly to $\alpha_1$-glycoproteins, was observed with tegaserod concentrations between 20 and 20000 µg/L (approximately 98%). The volume of distribution at steady state was about 368 L, indicating that the drug is distributed into the tissues [117].

In healthy volunteers and in patients with IBS-C and IBS with diarrhea (IBS-D), similar multiple-dose PK of tegaserod was observed, when the food effect was considered [117, 119, 122]. For the 6 mg BID dose in patients with IBS-C and IBS-D, $AUC_{\tau}$ and $C_{\text{max,ss}}$ were 30 to 50%, lower than those in healthy individuals following administration in fasting conditions [121]. For patients with IBS-C and IBS-D the type of bowel function abnormality has no impact on the PK of tegaserod (Table 4) [117, 119, 122-124].

Tegaserod dose adjustment is not required in patients with mild hepatic disease (caution recommended) and in patients with mild-moderate renal impairment. However, tegaserod is not
Table 2. PK of tegaserod in fasting and fed conditions.

| Treatment | Pharmacokinetic Parameters (mean ± SD, median for t_max and t_lag) |
|-----------|---------------------------------------------------------------|
|           | C_max (ng/mL) | AUC_0-∞ (ng*h/m) | t_max (h) | t1/2,z (h) | t_lag (h) | CL/F (L*h⁻¹) | Vz/F (L) | Vss (L) | F (%) |
| 12 mg p.o. fasted | 5.5 ± 2.2 | 17.1 ± 6.4 | 1.5 | 6.5 ± 3.2 | 0 | 799 ± 301 | 7350 ± 6147 | - | 11 ±4 |
| 12 mg p.o. fed | 2.5 ± 0.9 | 8.0 ± 2.6 | 2 | 7.2 ± 2.3 | 0.7 | 1995 ± 548 | 11821 ±1984 | - | - |
| 3 mg infusion§ fasted | 45.4 ± 9.2 | 40.0 ± 7.9 | - | 10.8 ± 4.6 | - | 77 ± 15* | 1149 ± 405* | 368 ±223 | - |

*F=1; § over 40 min. Data are referred to a study involving 12 healthy male subjects aged 19-31 years [116].

Table 3. Multiple-dose PK of tegaserod.

| Treatment (BID) | Pharmacokinetic Parameters (mean ± SD, median for t_max) |
|-----------------|----------------------------------------------------------|
|                 | C_max,ss (ng/mL) | AUC_τ (ng*h/mL) | t_max,ss (h) | C_min,ss (ng/mL) | Accumulation Ratio |
| 2 mg            | 0.7 ± 0.3 | 2.4 ±1.3 | 1 | < LOQ | 0.93 |
| 6 mg            | 2.7 ±1.2 | 8.9 ±4.2 | 0.8 | 0.11 ±0.07 | 1.16 |
| 12 mg (2x6 mg)  | 5.6 ±2.9 | 20.4 ±14.0 | 1 | 0.28 ±0.11 | 1.15 |

Data are referred to a study involving 18 subjects (11 male and 7 female) aged 21-36 years [121].

Table 4. PK of tegaserod in IBS-C patients.

| Treatment (BID) | Subjects | Pharmacokinetic Parameters (mean ± SD, median for t_max) |
|-----------------|----------|----------------------------------------------------------|
|                 |          | C_max,ss (ng/mL) | t_max,ss (h) | AUC_τ (ng*h/mL) |
| 6 mg tablets    | C-IBS patients* | 1.7 ± 0.7 | 1.0 | 5.7 ± 2.5 |
|                 | D-IBS patients* | 1.9 ± 1.4 | 1.0 | 4.8 ± 2.4 |
|                 | Healthy volunteers§ | 2.7 ± 1.2 | 0.8 | 8.9 ± 4.2 |

*Data are referred to a study involving 54 patients for C-IBS or 32 patients for D-IBS [122]; § Data are referred to a study involving 18 subjects (11 male and 7 female) [121].

recommended for patients with moderate-severe hepatic or severe renal impairments [117, 120].

4.2. Efficacy Data

Tegaserod accelerates gastric emptying and colonic transit time in healthy subject and in patients with IBS-C [26, 125-129].

Its efficacy was investigated in phase III clinical trials involving approximately 9000 IBS patients, mostly women with constipation-predominant symptoms. In the majority of studies, the clinical outcome was the Subject’s Global Assessment (SGA) of relief of overall GI symptoms [130].

Four pivotal Phase III RCTs [29, 30-32] evaluated tegaserod versus placebo. The results showed that tegaserod was significantly better than placebo at relieving overall and key individual IBS symptoms including abdominal pain and discomfort, bloating and constipation. Following the cessation of treatment with tegaserod, IBS symptoms slowly recurred, indicating that there was no rebound effect. Tack et al. [32], showed significant improvements in Quality of Life (QoL) and health economic-related outcomes. In all four pivotal studies, response to tegaserod was rapid, sustained, and increasing during the course of treatment.
Tegaserod efficacy was also evaluated in six phase IIb/IV studies in IBS patients worldwide [131-136]. Data from two of them [131, 134], with a similar design to the pivotal IBS trials, demonstrated that significantly more patients taking tegaserod experienced satisfactory relief of overall and individual symptoms (abdominal pain/discomfort, stool frequency, stool consistency, and straining during defecation) compared to placebo. These results confirm that tegaserod is an effective treatment irrespective of factors such as geographical region, race, and culture. In addition, two of these trials included patients without diarrhea (non-IBS-D), and indicated that tegaserod is effective in this subgroup of patients, as well as those with IBS-C according to the Rome II criteria [137].

In conclusion, results from clinical studies demonstrated that tegaserod at 6 mg BID is associated with significant relief, compared with placebo or baseline, of overall and individual symptoms in IBS-C and non-IBS-D patients [136, 138].

4.3. Safety Evaluation

4.3.1. Common Adverse Reactions

The frequency of reported adverse reactions in the 3-month trials with tegaserod varies considerably (e.g. 50-60% of US patients reported adverse reactions), whereas only 4% of the patients in an Asia-Pacific trial and 38% (13% drug-related) in a European trial did so. As this can be explained neither by different doses nor by trial design, cultural differences in the willingness to complain are the most likely explanation. The most common adverse reactions were diarrhea, headache and abdominal pain and were graded as mild, sometimes as moderate. Only diarrhea was reproducibly more prevalent in the tegaserod than in the placebo groups, but this was not dose-related. Three adverse reactions potentially attributable to tegaserod have gained particular attention, namely an increased rate of abdominal surgery, ischemic colitis and cardiac events. They occurred so infrequently that they are unlikely to be identified in Phase III trials and may only come up in pooled analyses or during post-marketing surveillance, but they are severe enough to warrant concerns [32, 33].

Less common adverse reactions reported in ≤ 2% of patients in clinical trials of IBS-C on tegaserod but more frequently than placebo affect: blood and lymphatic system (anemia); ear and labyrinth (vertigo); gastrointestinal apparatus (rectal hemorrhage); musculoskeletal and connective tissue (arthropathy, tendonitis); nervous system (migraine); asthenia; increased blood creatine phosphokinase; increased appetite.

4.3.2. Gastrointestinal and CNS Effects

Gastrointestinal (GI) symptoms are the most common side effects. In pooled data from Phase III RCTs in IBS-C, diarrhea was reported by 8.8% of patients treated with tegaserod 6 mg BID versus 3.8% of patients on placebo, and similar rates were present in international post-US marketing RCTs. Diarrhea occurred mainly in the first week of treatment and was often transient, resolving with continued treatment. Tegaserod-induced diarrhea was mild in many patients, without fluid or electrolyte disturbances, and less than 3% of patients discontinued tegaserod due to diarrhea. The incidence of other GI symptoms (e.g. abdominal pain, nausea and flatulence) was similar between tegaserod and placebo. Regarding abdominal surgery in patients with IBS-C, a pooled analysis of Phase III and post-US marketing RCT did not demonstrate any significant difference between tegaserod (0.44%) and placebo (0.41%) in the incidence of abdominal/pelvic surgery [139]. Patients with IBS have a higher risk of developing colonic ischemia than the general population. Episodes of ischemic colitis were not reported with tegaserod in over 11600 patients participating in Phase III or post-marketing RCTs. In the post-marketing surveillance, the rate of ischemic colitis with tegaserod was lower than that observed in non-tegaserod patients since post-marketing reports have noted that incidence of cases of ischemic colitis and intestinal ischemia in patients taking tegaserod appears to be similar to the general population and is less than estimates for the IBS patient population. Moreover, no mechanism has been identified through which tegaserod might predispose to ischemic colitis [32, 77, 78].

Pooled analysis of Phase III RCTs demonstrated an increase in the incidence of headaches in tegaserod-treated (6 mg BID) vs. placebo-treated patients (15% vs. 12.3%, respectively; P < 0.05). However, post-US marketing RCTs did not show this increased incidence [77, 78].
The last FDA revision (March 2019) reports in “Warning and Precaution” section the following: “Monitor patients for the clinical worsening of depression and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment. Instruct patients to immediately discontinue Zelnorm™ and contact their healthcare provider if their depression is persistently worse or they are experiencing emergent suicidal thoughts or behaviors”. Indeed, suicide, suicidal attempt and ideation, and self-injurious behavior have been reported in clinical trials of IBS-C and other gastrointestinal motility disorders. The frequency of suicidal ideation or attempts with tegaserod treatment (8 patients out of 10,003) was higher than placebo (1 patient out of 5,425). Events on tegaserod included one completed suicide, two suicide attempts, four cases of self-injurious behavior, and one case of suicidal ideation. There was one suicide attempt on placebo. Of the eight tegaserod-treated patients who experienced an event, all were less than 65 years of age, seven were female and three had IBS-C. The patient who committed suicide was a female, less than 65 years of age with IBS-C, taking tegaserod 2 mg twice daily. Suicidal ideation/behavior in clinical trials was proportionately more frequent among patients receiving antidepressant medication [33].

4.3.3. Cardiovascular Effects

Until 2007, many studies on both healthy volunteers and patients with IBS-C treated with tegaserod did not demonstrated incidence of ventricular/supraventricular tachycardia, or clinically significant effects on cardiac repolarization and QT interval duration [29, 140]. The administration of i.v. tegaserod (0.8-20 mg) in 36 healthy volunteers resulted in plasma concentrations up to 100 times those measured after therapeutic doses (6 mg orally BID; maximum 5 ng/mL), but did not affect any ECG parameter, including QT interval duration. Furthermore, patients on placebo or oral tegaserod (2 or 6 mg BID), showed similar changes in ECG parameters, QT interval duration, and similar frequency and type of arrhythmias during therapy [141].

In 2007, the FDA requested withdrawal from the market, citing a relationship between prescriptions of tegaserod and increased risks of heart attack or stroke [142]. Novartis Pharmaceuticals denies an association as all affected patients were said to have pre-existing cardiovascular disease or risk factors for such. Thus, no causal relationship between tegaserod use and cardiovascular events had been demonstrated. Indeed, a matched case-control study of tegaserod-treated patients with untreated patients found no association between tegaserod and adverse cardiovascular outcomes [143]. Nevertheless, in 2007 a pooled retrospective analysis of ischemic events from 29 clinical studies using tegaserod in a variety of GI tract conditions [144, 145] allowed to recognize the adverse events that the Phase III clinical trials were not powered to detect. Indeed, the prevalence of cardiovascular adverse events with tegaserod was low and likely to fall below the limit of detection in a clinical trial programme. These studies included 11614 tegaserod-treated patients and 7031 treated with placebo (average age: 43 years; 88% women). Thirteen tegaserod treated patients (0.11%) had serious and life-threatening cardiovascular events. Among these, four patients had a myocardial infarction (one died), six had severe cardiac ischemia, and three had a stroke [142]. Among patients on placebo, only one had symptoms suggesting a stroke. This patient recovered without complications. Three adjudications, one internal (by the developer) and two external, attested the limitations in data collections. The internal one counted 18 patients with cardiovascular events for tegaserod and 2 for placebo. The second, by NY’s Mt. Sinai Hospital, counted 13 for tegaserod and 1 for placebo and identified an imbalance in patients taking tegaserod (0.1%) compared to placebo (0.01%). The third, by Duke Clinical Research Institute, counted 7 for tegaserod and 1 for placebo and was conducted with additional patient-level information, confirming an imbalance in cardiovascular events in patients taking tegaserod compared to placebo. All events occurred in male and female patients with a history of cardiovascular ischemic disease and/or more than one cardiovascular risk factor. The patient narratives and tabulations in the briefing documents for the 2018 FDA advisory committee meeting confirm the inadequacy of the data collection [146, 147]. With better data collection, multiple adjudications would not have been necessary, or the repeat adjudica-
tions would have been more consistent. Regardless, the adjudications all support that there is an increased cardiovascular risk with tegaserod but of an unknown magnitude.

The mechanism through which tegaserod use may be associated with increased cardiovascular risk is not clearly established. A hypothetical mechanism for tegaserod-related cardiac events was proposed involving interaction with receptors other than 5-HT4. Indeed, tegaserod shows moderate activity for 5-HT2b or 5-HT1b/d receptor subtypes on coronary arterioles [148]. In fact, these receptors are located on vascular smooth muscle and endothelial cells causing contraction of human coronary arteries. Regarding 5-HT1d, a single dose of the selective agonist PNU-142633 produced chest pain in 2 of 34 migraine patients in a double-blind, placebo-controlled study [149]. Regarding 5-HT1b, activation of which produces coronary vasoconstriction, tegaserod is a significantly more potent agonist at the 124 Cys-variant than at the wild-type 5-HT1b receptor [150]. However, as tegaserod does not behave as a 5-HT1b receptor agonist in a recent study of human isolated proximal and distal coronary arterioles, the mechanisms involved remain unclear [151]. Furthermore, platelets have 5-HT receptors. Although there are variations in the studies of tegaserod effects upon platelets, one study strongly suggests that tegaserod increases platelet aggregation [152]. Tegaserod has no affinity for 5-HT3 or dopamine receptors.

4.3.4. Postmarketing Data

FDA approved tegaserod in 2002 for women with predominant IBS-C and in 2004 for patients up to 65 years of age with chronic idiopathic constipation (CIC) under the name of Zelnorm® (marketed by Novartis). FDA asked Novartis to suspend its U.S. marketing and sales on March 30, 2007, due to increased incidence of heart attack, stroke, and unstable angina (heart/chest pain) in patients treated with tegaserod compared with placebo [145]. FDA concluded that for most patients the benefits of this drug no longer outweighed the risks. Novartis no longer provided Zelnorm® and since 2009 agreed to continue to supply tegaserod in the U.S. only for emergency use (immediate life-threatening or serious conditions enough to qualify for hospitalization) [153, 154]. Tegaserod was also approved in several other countries for the treatment of IBS-C and CIC. However, in March 2007 it was withdrawn from most markets [141]. Tegaserod never received approval in the European Union (EU) [155]. India banned tegaserod in March 2011, because of a 10-fold increase risk in heart attack and stroke [156]. Tegaserod was resubmitted in 2018 to the FDA for use in women having irritable bowel syndrome with constipation and low cardiovascular risk. An advisory committee meeting for the resubmission was held on October 17, 2018, with the members voting 11 to 1 in favor of approval [28, 33].

The following adverse reactions have been identified during post-approval use of Zelnorm®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure [33]:

- Ischemic colitis, mesenteric ischemia, gangrenous bowel and rectal bleeding;
- Severe diarrhea resulting in syncope, hypotension, hypovolemia, electrolyte disorders;
- Sphincter of Oddi spasm, bile duct stone, cholecystitis with elevated transaminases, elevation in ALT, AST and bilirubin, hepatitis;
- Alopecia;
- Hypersensitivity reactions, including anaphylaxis.

4.3.5. Safety in Special Populations

Available data from case reports with tegaserod use in pregnant women has not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal studies, decreased survival of rat pups was observed with maternal dietary administration of tegaserod at 71 times the recommended dose during organogenesis and through lactation. Decreased body weight and delays in developmental landmarks in rat pups were observed with maternal dietary administration of tegaserod at 45 times the recommended dose. No adverse developmental effects were observed with oral administration of tegaserod to
pregnant rats at doses up to 15 times the recommended dose or to pregnant rabbits at doses up to 51 times the recommended dose during organogenesis [33].

There are no data regarding the presence of tegaserod in human milk, the effects on the breastfed infant, or the effects on milk production. Tegaserod and its metabolites are present in rat milk; the milk to plasma concentration ratio for tegaserod is very high. Following oral administration, tegaserod and its metabolites are excreted in the milk of lactating rats with a milk:plasma concentration ratio of 33:1. Since when a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious reactions in the breastfed infant, including tumorigenicity, advise a lactating woman that breastfeeding is not recommended during treatment with tegaserod [33].

Safety and effectiveness of tegaserod in pediatric patients have not been established. Moreover, tegaserod is not indicated in patients 65 years of age and older [33].

No change in the pharmacokinetics of tegaserod was observed in subjects with end-stage renal disease requiring hemodialysis. Although renal impairment does not affect the pharmacokinetics of tegaserod, the pharmacokinetics of its main metabolite M29.0 are altered, its $C_{\text{max}}$ doubling and the AUC increasing 10-fold in patients with severe renal impairment compared to healthy subjects with normal renal function. Thus, tegaserod is contraindicated in patients with severe renal impairment or end-stage renal disease. Differently, no dosage adjustment is recommended in patients with mild to moderate renal impairment [33].

In subjects with mild hepatic impairment (Child-Pugh A), the mean tegaserod AUC was 31% higher and the $C_{\text{max}}$ was 16% higher compared to healthy subjects with normal hepatic function. The increase in exposure in subjects with mild impairment is not considered to be clinically relevant. Only in a single subject with moderate hepatic impairment, the $C_{\text{max}}$ and AUC were 140% and 200% of that observed in healthy controls. Thus, no tegaserod dosage adjustment is necessary in patients with mild hepatic impairment (caution recommended). Tegaserod has not been studied in patients with moderate or severe hepatic impairment (Child-Pugh B or C) and it is, therefore, contraindicated in these patients [33, 117, 120].

4.3.6. Major Changes after Resubmission

After the proposal to remarket tegaserod in 2018, the FDA supported its reintroduction on the market. To ensure a favorable benefit-risk, the reintroduction proposal focuses both on a single indication (IBS-C) and a restricted patient population that is females 65 and younger affected by IBS-C without a history of ischemic cardiovascular disease [146].

In particular, the sponsor’s proposal is supported by:

- Clinical trial data, epidemiology study findings and mechanistic evaluations that support a favorable cardiovascular safety profile. While the available evidence supports cardiovascular safety, the data are insufficient to rule out possibilities of low risk associated with tegaserod that was observed in the initial signal which was driven by a small number of events across controlled studies;

- Clear demonstration of effectiveness across large and well-designed studies, with a meaningful response in overall impact assessment and improvement in key symptoms;

- Evaluations of more than 6,000 IBS-C patients, as well as data from other studied populations and postmarketing experience supporting good tolerability and a favorable safety profile.

Because there could be residual uncertainty around the cardiovascular risk associated with tegaserod, the sponsor proposed its reintroduction in a restricted population based on age, gender and cardiovascular disease history. The proposed age and gender restrictions are consistent with patients that have inherently lower cardiovascular risk than the general population and consistent with the natural history of IBS-C, as well as the majority of the clinical trial experience, predominantly comprised of working-age women. In addition, any risk will likely be reduced by contraindicating use in individuals with pre-existing ischemic cardiac or cerebral diseases since such patients would be
at greatest risk for a cardiac or ischemic event. This approach would make tegaserod available to many IBS-C patients who may benefit from availability of an additional effective treatment option and who are at an inherently lower risk for a cardiovascular event than the broader population [147].

The last version of prescribing information of Zelnorm™ (the brand name for tegaserod marketed by Novartis) revised by FDA on March 2019 reports several changes as follows [33]:

- **Indications and Usage:** Zelnorm™ is a serotonin-4 (5-HT₄) receptor agonist indicated for the treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation (IBS-C). Limitations of Use: the safety and effectiveness of Zelnorm™ in men with IBS-C have not been established. In two randomized, placebo-controlled, double-blind trials enrolling 288 males, efficacy response rates were similar between Zelnorm™ and placebo in the male subgroup;

- **Contraindications:** Zelnorm™ is contraindicated in patients with a history of myocardial infarction, stroke, transient ischemic attack, or angina; a history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment (eGFR <15 mL/min/1.73 m²) or end-stage renal disease; moderate or severe hepatic impairment (Child-Pugh B or C); history of bowel obstruction, symptomatic gallbladder disease; suspected sphincter of Oddi dysfunction, or abdominal adhesions; hypersensitivity to tegaserod.

- **Warnings and Precautions:** Cardiovascular Ischemic Events, Including Major Adverse Cardiovascular Events (MACE): The potential risks of treatment must be balanced with expectations in improvements in symptoms of IBS-C. Discontinue Zelnorm™ treatment in patients who experience a myocardial infarction, stroke, transient ischemic attack or angina. Evaluate the risks and benefits of continued treatment in patients who develop clinical or other evidence of cardiovascular ischemic heart disease and/or experience changes in health status that could increase cardiovascular risk during treatment. Ischemic Colitis: Monitor for rectal bleeding, bloody diarrhea, and new or worsening abdominal pain and discontinue Zelnorm™ if symptoms develop. Volume Depletion Associated with Diarrhea: Avoid use in patients with severe diarrhea. Instruct patients to discontinue Zelnorm™ and contact their healthcare provider if severe diarrhea, hypotension or syncope occur. Suicidal Ideation and Behavior: Monitor patients for clinical worsening of depression and the emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment. Instruct patients to immediately discontinue Zelnorm™ and contact their healthcare provider if their depression is persistently worse or they are experiencing emergent suicidal thoughts or behaviors.

**CONCLUSION**

The complex nature of IBS is still a significant treatment challenge for patients and physicians. Traditional medications are frequently prescribed with deceiving results in IBS patients. Increasing knowledge in IBS pathophysiology has led to the development of several new compounds as serotonergic medications such as tegaserod that have effectively managed many of the motor and sensory abnormalities in IBS.

Preclinical and clinical studies have demonstrated that tegaserod accelerates gastric emptying and colonic transit time. Dose adjustment is not required in patients with mild hepatic disease and with mild-moderate renal impairment, while it is not recommended in patients with moderate-severe hepatic and severe renal impairments. Data from international clinical trials suggested that tegaserod provides rapid, sustained, and statistically significant relief of IBS overall and individual symptoms (abdominal pain/discomfort, bloating, and constipation) compared with placebo. Efficacy of tegaserod was also confirmed in open-label trials performed in real-life clinical settings. Tegaserod is associated with significant improvements in patients’ QoL and work productivity.
Despite its clinical efficacy, data collected demonstrated cardiovascular adverse events. Therefore, the FDA requested a market withdrawal, citing a relationship between the drug and increased risks of heart attack or stroke. Nevertheless, the manufacturer denied this and a causal relationship between tegaserod use and cardiovascular events was not demonstrated. Indeed, both patients follow-up and cardiovascular adverse events description were incomplete. Therefore, the inadequacy of the data collection was confirmed such that an accurate estimation of adverse events is not possible because its magnitude remains unknown, even though an increase in cardiovascular risk seems to exist. As concerns the clinical use of tegaserod, the proposal to remarket the drug is not irrational because the absolute risk is low in patients who otherwise have negligible risk. However, the pharmacology, the clinical trial results and the cardiac risk magnitude of tegaserod still remain uncertain.

**LIST OF ABBREVIATIONS**

| Abbreviation | Full Form |
|--------------|-----------|
| 5-HT         | Serotonin |
| 5-HT₄R       | 5-HT₄ receptor |
| BID          | Twice a Day |
| CGRP         | Calcitonin Gene-Related Peptide |
| CIC          | Chronic Idiopathic Constipation |
| DSS          | Dextran Sodium Sulfate |
| FD           | Functional Dyspepsia |
| FDA          | Food and Drug Administration |
| GI           | Gastrointestinal |
| IBS          | Irritable Bowel Syndrome |
| IBS-C        | Irritable Bowel Syndrome with Constipation |
| IBS-D        | Irritable Bowel Syndrome with Diarrhea |
| PAG          | Pentylaminoguanidine |
| PK           | Pharmacokinetic |
| QoL          | Quality of Life |
| RCT          | Randomized Controlled Trial |
| SP           | Substance P |
| TNBS         | Trinitrobenzene Sulfonic Acid |

**CONSENT FOR PUBLICATION**

Not applicable.

**FUNDING**

None.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

**ACKNOWLEDGEMENTS**

All individuals listed as authors have contributed to the data collection and in drafting the paper.

**REFERENCES**

[1] Lovell, R.M.; Ford, A.C. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin. Gastroenterol. Hepatol., 2012, 10(7), 712-721.e4.

[2] Moayyedi, P.; Andrews, C.N.; MacQueen, G.; Korownyk, C.; Marsiglio, M.; Graff, L.; Kvern, B.; Lazarescu, A.; Liu, L.; Paterson, W.G.; Sidani, S.; Vanner, S. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). J. Can. Assoc. Gastroenterol., 2019, 2(1), 6-29.

[3] Moayyedi, P.; Marsiglio, M.; Andrews, C.N.; Graff, L.A.; Korownyk, C.; Kvern, B.; Lazarescu, A.; Liu, L.; MacQueen, G.; Paterson, W.G.; Sidani, S.; Vanner, S.J.; Sinclair, P.; Marshall, L.; Fernandes, A. Patient engagement and multidisciplinary involvement has an impact on clinical guideline development and decisions: a comparison of two irritable bowel syndrome guidelines using the same data. J. Can. Assoc. Gastroenterol., 2019, 2(1), 30-36.

[4] Faresjö, Å.; Walter, S.; Norlin, A.K.; Faresjö, T.; Jones, M.P. Gastrointestinal symptoms - an illness burden that affects daily work in patients with IBS. Health Qual. Life Outcomes, 2019, 17(1), 113.
Evans, B.W.; Clark, W.K.; Moore, D.J.; Whorwell, P.J. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. *Cochrane Database Syst. Rev.*, 2007, 4(4), CD003960. http://dx.doi.org/10.1002/14651858.CD003960.pub3 PMID: 17943807

Rivkin, A. Tegaserod maleate in the treatment of irritable bowel syndrome: a clinical review. *Clin. Ther.*, 2003, 25(7), 1952-1974. http://dx.doi.org/10.1016/S0149-2918(03)80198-4 PMID: 12946544

Rossi, S. *Australian Medicines Handbook*, AMH Pty Ltd: Australia; 27th ed., 2004.

Marciniak, T.A.; Serebruany, V. Should we use tegaserod for irritable bowel syndrome? *Am. J. Ther.*, 2019, 26(3), e417-e420. http://dx.doi.org/10.1097/MJT.0000000000000947 PMID: 30946048

Morganroth, J.; Ruegg, P.C.; Dunger-Baldauf, C.; Appel-Dingemans, S.; Bliesath, H.; Lefkowitz, M. Tegaserod, a 5-hydroxytryptamine type 4 receptor partial agonist, is devoid of electrocardiographic effects. *Am. J. Gastroenterol.*, 2002, 97(9), 2321-2327. http://dx.doi.org/10.1111/j.1572-0241.2002.05986.x PMID: 12358251

Müller-Lissner, S.; Holtmann, G.; Rueegg, P.; Weidinger, G.; Löfler, H. Tegaserod is effective in the initial and retreatment of irritable bowel syndrome with constipation. *Aliment. Pharmacol. Ther.*, 2005, 21(1), 11-20. http://dx.doi.org/10.1111/j.1365-2036.2004.02294.x PMID: 15644040

Novick, J.; Miner, P.; Krause, R.; Glebas, K.; Bliesath, H.; Ligozio, G.; Ruegg, P.; Lefkowitz, M. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment. Pharmacol. Ther.*, 2002, 16(11), 1877-1888. http://dx.doi.org/10.1046/j.1365-2036.2002.01372.x PMID: 12390096

Tegaserod, N.D.A. 21-200 *Supplements*. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021200Orig1s015lbl.pdf [Accessed May 17, 2019].

Tegaserod for the Treatment of Irritable Bowel Syndrome  
Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2020, Vol. 19, No. 4 363

http://dx.doi.org/10.1038/sj.bjp.0705929 PMID: 15466450

De Maeyer, J.H.; Lefebvre, R.A.; Schuurkes, J.A. 5-HT4 receptor agonists: similar but not the same. *Neurogastroenterol. Motil.*, 2008, 20(2), 99-112. http://dx.doi.org/10.1111/j.1365-2982.2007.01059.x PMID: 18199093

Tegaserod, N.D.A. 38 *Supplements*. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021200Orig1s015lbl.pdf [Accessed May 17, 2019].

http://dx.doi.org/10.1053/j.gastro.2016.07.032 PMID: 27480173

Spohn, S.N.; Bianco, F.; Scott, R.B.; Keenan, C.M.; McNaughton, W.K.; De Giorgio, R.; Harkey, K.A.; Maue, G.M. Protective actions of epithelial 5-hydroxytryptamine 4 receptors in normal and inflamed colon. *Gastroenterology*, 2016, 151(5), 933-944.e3. http://dx.doi.org/10.1053/j.gastro.2016.07.032 PMID: 27480173

Sun, Y.N.; Luo, J.Y. Effects of tegaserod on Fos, substance P and calcitonin gene-related peptide expression induced by colon inflammation in lumbar-sacral spinal cord. *World J. Gastroenterol.*, 2004, 10(12), 1830-1833. http://dx.doi.org/10.3748/wjg.v10.i12.1830 PMID: 15188517

Crowell, M.D. Role of serotonin in the pathophysiology of the irritable bowel syndrome. *Br. J. Pharmacol.*, 2004, 141(8), 1285-1293. http://dx.doi.org/10.1038/sj.bjp.0705762 PMID: 15100164

Hegde, S.S.; Eglen, R.M. Peripheral 5-HT4 receptors. *FASEB J.*, 1996, 10(12), 1398-1407. http://dx.doi.org/10.1096/fasebj.10.12.8903510 PMID: 8903510

Mawe, G.M.; Hoffman, J.M. Serotonin signalling in the gut–functions, dysfunctions and therapeutic targets. *Nat. Rev. Gastroenterol. Hepatol.*, 2013, 10(8), 473-486.
Bertrand, P.P. Real-time detection of serotonin release from enterochromaffin cells of the guinea-pig ileum. *Neurogastroenterol. Motil.*, 2004, 16(5), 511-514. http://dx.doi.org/10.1111/j.1365-2982.2004.00572.x PMID: 15500507

Hoffman, J.M.; Tyler, K.; MacEachern, S.J.; Balember, O.B.; Johnson, A.C.; Brooks, E.M.; Zhao, H.; Swain, G.M.; Moses, P.L.; Galligan, J.J.; Sharkey, K.A.; Greenwood-Van Meerveld, B.; Maue, G.M. Activation of colonic mucosal 5-HT(4) receptors accelerates propulsive motility and inhibits visceral hypersensitivity. *Gastroenterology*, 2012, 142(4), 844-854.e4. http://dx.doi.org/10.1053/j.gastro.2011.12.041 PMID: 22226658

Scott, L.J.; Perry, C.M. Tegaserod. *Drugs*, 1999, 58(3), 491-496. http://dx.doi.org/10.2165/00003495-199958030-00013 PMID: 10493276

Saad, R.; Chey, W.D. Tegaserod in the treatment of irritable bowel syndrome with constipation. *Womens Health (Lond)*, 2006, 2(1), 29-42. http://dx.doi.org/10.2217/17455057.2.1.29 PMID: 19803924

Jadallah, K.A.; Kullab, S.M.; Sanders, D.S. Constipation-predominant irritable bowel syndrome: a review of current and emerging drug therapies. *World J. Gastroenterol.*, 2014, 20(27), 8898-8909. PMID: 25083062

Taniyama, K.; Nakayama, S.; Takeda, K.; Matsuyma, S.; Shirakawa, J.; Sano, I.; Tanaka, C. Cisapride stimulates motility of the intestine via the 5-hydroxytryptamine receptors. *J. Pharmacol. Exp. Ther.*, 1991, 258(3), 1098-1104. PMID: 1890614

Edwards, C.A.; Holden, S.; Brown, C.; Read, N.W. Effect of cisapride on the gastrointestinal transit of a solid meal in normal human subjects. *Gut*, 1987, 28(1), 13-16. http://dx.doi.org/10.1136/gut.28.1.13 PMID: 3817579

Krevsky, B.; Malmud, L.S.; Maurer, A.H.; Somers, M.B.; Siegel, J.A.; Fisher, R.S. The effect of oral cisapride on colonic transit. *Aliment. Pharmacol. Ther.*, 1987, 1(4), 293-304. http://dx.doi.org/10.1111/j.1365-2036.1987.tb00629.x PMID: 2979674

Farup, P.G.; Hovdenak, N.; Wetterhus, S.; Lange, O.J.; Hovde, O.; Trondstad, R. The symptomatic effect of cisapride in patients with irritable bowel syn-

drome and constipation. *Scand. J. Gastroenterol.*, 1998, 33(2), 128-131. http://dx.doi.org/10.1080/00365529850166833 PMID: 9517521

Lewis, C. The impact of direct-to-consumer advertising. *FDA Consum.*, 2003, 37(2), 8. PMID: 12715762

De Knaep, A.G.M.; Moens, L.J.R.; Rey, M. Synthesis of cisapride. *International Patent WO/1998/016511*, 1998 April 23.

Palmer, R.M.J.; Meyers, N.L.; Knight, J. Process for the preparation of renzapride and intermediates thereof. *European Patent EP1664048 (A2)*, 2006 June 07.

Lee, M.J.; Choi, S. Im. W-5-HT4 Receptor agonists in the treatment of gastrointestinal motility disorders: current status and perspective. *Int. J. Gastroenterol. Disorder*, 2014, 1, 108-115.

Noverola, A.V.; Soto, J.P.; Spickett, R.G.W. Aromatic amidines of heterocyclic compounds and therapeutic compositions containing same. U.S. Patent 4,138,492, 1979 February 6.

Vukics, K.; Fischer, J.; Lévi, S.; Erdélyi, P. Process for the synthesis of mosapride. *International Patent WO/2003/106440*, 2003 December 24.

Coremans, G.; Kerstens, R.; De Pauw, M.; Stevens, M. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial. *Digestion*, 2003, 67(1-2), 82-89. http://dx.doi.org/10.1159/000070202 PMID: 12743445

Chai, Y.; Xu, D.; Gong, Y.; Zheng, L.; Qian, W.; Yang, Z.; Tian, Z.; Lv, F.; Yuan, F. Synthesis process of prucalopride. *Chinese Patent CN103664912*, 2014 March 26.

Long, D.D.; Armstrong, S.R.; Beattie, D.T.; Choi, S.K.; Fatheree, P.R.; Gendron, R.A.; Genov, D.; Goldblum, A.A.; Humphrey, P.P.; Jiang, L.; Marquess, D.G.; Shaw, J.P.; Smith, J.A.; Turner, S.D.; Vickery, R.G. Discovery, oral pharmacokinetics and clinical efficacy of velusetrag, a highly selective 5-HT(4) receptor agonist that has achieved proof-of-concept in patients with chronic idiopathic constipation. *Bioorg. Med. Chem. Lett.*, 2012, 22(19), 6048-6052. http://dx.doi.org/10.1016/j.bmccl.2012.08.051 PMID: 22959244

Henschke, J.P.; Liu, Y.; Xia, L.; Chen, Y.F. Process for the preparation of lubiprostone. U.S. Patent 8,846,958 B2, 2014 September 30.

Chen, X.; Wu, J.; Mi, P.; Tao, A.; Yuan, J. Preparation method of plecanatide. *Chinese Patent CN104211777*, 2014 December 17.
[67] Starke, I.; Dahlstrom, M.; Blomberg, D. Chemical compounds. *International Patent WO/2002/050051*, 2002 June 27.

[68] American Gastroenterological Association medical position statement: Irritable bowel syndrome. *Gastroenterol.*, 2002, 123, 2105-2107. http://dx.doi.org/10.1053/gast.2002.37095b

[69] Frissora, C.L. A new look at irritable bowel syndrome [IBS]: a neuroenteric disorder. *Compr. Ther.*, 2002, 29(3), 222-231. http://dx.doi.org/10.10109/s12019-002-0031-y PMID: 12360634

[70] Poynard, T.; Naveau, S.; Mory, B.; Chaput, J.C. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment. Pharmacol. Ther.*, 1994, 8(5), 499-510. http://dx.doi.org/10.1111/j.1365-2036.1994.tb00322.x

[71] Camilleri, M. Management of the irritable bowel syndrome. *Gastroenterology*, 2001, 120(3), 652-668. http://dx.doi.org/10.1053/gast.2001.21908 PMID: 11179242

[72] Quigley, E.M. Cisapride: what can we learn from the rise and fall of a prokinetic? *J. Dig. Dis.*, 2011, 12(3), 147-156. http://dx.doi.org/10.1011/j/j.1751-2980.2011.00491.x PMID: 21615867

[73] World Health Organization. *Pharmaceuticals: restrictions in use and availability*. Available from: https://apps.who.int/medicinedocs/pdf/s2203e/s2203e.pdf (Accessed May 17, 2019).

[74] Meyers, N.L.; Hickling, R.I. The cardiovascular safety profile of renzapride, a 5-HT3 receptor antagonist and 5-HT4 agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am. J. Gastroenterol.*, 2009, 104(7), 1831-1843. http://dx.doi.org/10.1038/ajg.2009.223 PMID: 19471254

[75] Schaefer, P. Review article: the safety profile of tegaserod. *Aliment. Pharmacol. Ther.*, 2004, 20(Suppl. 7), 25-30. http://dx.doi.org/10.1111/j.1365-2036.2004.02182.x PMID: 15521852

[76] Hasler, W.L.; Schaefer, P. Safety profile of tegaserod, a 5-HT4 receptor agonist, for the treatment of irritable bowel syndrome. *Drug Saf.*, 2004, 27(9), 619-631. http://dx.doi.org/10.2165/0002018-200427090-00001 PMID: 15230644

[77] Shaw, A.; Camilleri, M.; Kolar, G.; Erwin, P.; West, C.P.; Murad, M.H. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag or naronapride) in chronic constipation. *Aliment. Pharmacol. Ther.*, 2014, 39(3), 239-253. http://dx.doi.org/10.1111/apt.12571 PMID: 24308797

[78] Sun, J.; Yuan, Y.Z.; Holtmann, G. Itopride in the treatment of functional dyspepsia in Chinese patients: a prospective, multicentre, post-marketing observational study. *Clin. Drug Investig.*, 2011, 31(12), 865-875. http://dx.doi.org/10.1007/BF03256924 PMID: 22035464

[79] Barish, C.F.; Drossman, D.; Johanson, J.F.; Ueno, R. Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig. Dis. Sci.*, 2010, 55(4), 1090-1097. http://dx.doi.org/10.10107/s10620-009-1068-x PMID: 20012484

[80] Rao, S.; Lembo, A.J.; Shiff, S.J.; Lavins, B.J.; Currie, M.G.; Jia, X.D.; Shi, K.; MacDougall, J.E.; Shao, J.Z.; Eng, P.; Fox, S.M.; Schneider, H.A.; Kurtz, C.B.; Johnston, J.M. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am. J. Gastroenterol.*, 2012, 107(11), 1714-1724. http://dx.doi.org/10.1038/ajg.2012.255 PMID: 22986440

[81] Lacy, B.E.; Levenick, J.M.; Crowell, M. Chronic constipation: new diagnostic and treatment approaches. *Therap. Adv. Gastroenterol.*, 2012, 5(4), 233-247. http://dx.doi.org/10.1177/1756283X12443093 PMID: 22778789

[82] Rao, A.S.; Wong, B.S.; Camilleri, M.; McKinzie, S.; Burton, D.; Carlson, P.; Lamsam, J.; Singh, R.; Zinsmeister, A.R. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. *Gastroenterology*, 2010, 139(5), 1549-1558.e1. http://dx.doi.org/10.1053/j.gastro.2010.07.052 PMID: 20691689

[83] Wong, B.S.; Camilleri, M.; McKinzie, S.; Burton, D.; Graffner, H.; Zinsmeister, A.R. Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. *Am. J. Gastroenterol.*, 2011, 106(12), 2154-2164. http://dx.doi.org/10.1038/ajg.2011.285 PMID: 21876564

[84] Low, K.; Hwang, L.; Hua, J.; Zhu, A.; Morales, W.; Pimentel, M. A combination of rifaximin and neomycin is most effective in treating irritable bowel syndrome patients with methane on lactulose breath test. *J. Clin. Gastroenterol.*, 2010, 44(8), 547-550.
PMID: 19996983
[87] Gaitonde, A.; Mnoajkumar, B.; Sonawane, S. Synthesis of tegaserod or a salt thereof. *U.S. Patent 2009/036170 A1*, 2009 December 10.

[88] Zimmermann, A.E. Tegaserod: a 5-HT4 agonist for women with constipation-predominant irritable bowel syndrome. *Fomulary*, 2002, 37, 449-461.

[89] Pfannkuche, H.J.; Buhl, T.; Game, R.; Hoyer, D.; Mattes, H.; Buchheit, K.H. The properties of a new prokinetically active drug, SDZ HTF 919. *Neurogastroenterol Motil.*, 1995, 7, 280.

[90] Sanger, G.J.; Wardle, K.A.; Shapcott, S.; Yee, F.K. Constipation evoked by 5-HT3 receptor antagonists. *Serotonin: molecular biology, receptors and functional effects*, Springer Nature Switzerland: Birkhäuser Basel, 1991, pp. 381-388.

[91] Sowers, J.R.; Sharp, B.; McCallum, R.W. Effect of domperidone, an extracerebral inhibitor of dopamine receptors, on thyrotropin, prolactin, renin, aldosterone, and 18-hydroxycorticosterone secretion in man. *J. Clin. Endocrinol. Metab.*, 1982, 54(4), 869-871. http://dx.doi.org/10.1210/jcem-54-4-869

PMID: 7037817

[92] Burks, T.F.; Long, J.P. Catecholamine-induced release of 5-hydroxytryptamine (5-HT) from perfused vasculature of isolated dog intestine. *J. Pharm. Sci.*, 1966, 55(12), 1383-1386. http://dx.doi.org/10.1002/jps.2600551211

[93] Grider, J.R.; Foxx-Orenstein, A.E.; Jin, J.G. 5-Hydroxytryptamine4 receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. *Gastroenterology*, 1998, 115(2), 370-380. http://dx.doi.org/10.1016/S0016-5085(98)70203-3

PMID: 9679042

[94] Jin, J.G.; Foxx-Orenstein, A.E.; Grider, J.R. Propulsion in guinea pig colon induced by 5-hydroxytryptamine (HT) via 5-HT4 and 5-HT3 receptors. *J. Pharmacol. Exp. Ther.*, 1999, 288(1), 93-97. http://dx.doi.org/10.1124/jpet.103.053256

PMID: 9862758

[95] Nguyen, A.; Camilleri, M.; Kost, L.J.; Metzger, A.; Sarr, M.G.; Hansen, R.B.; Fett, S.L.; Zinsmeister, A.R. SDZ HTF 919 stimulates canine colonic motility and transit in vivo. *J. Pharmacol. Exp. Ther.*, 1997, 280(3), 1270-1276.

PMID: 9067313

[96] Schikowski, A.; Thewissen, M.; Mathis, C.; Ross, H.G.; Enck, P. Serotonin type-4 receptors modulate the sensitivity of intramural mechanoreceptive afferents of the cat rectum. *Neurogastroenterol Motil.*, 2002, 4(3), 221-227. http://dx.doi.org/10.1046/j.1365-2982.2002.00328.x

PMID: 12061906

[97] Coelho, A.M.; Rovira, P.; Fioramonti, J.; Bueno, L. Antinociceptive properties of HTF 919 (tegaserod), a 5-HT4 receptor partial agonist, on colorectal distension in rats. *Gastroenterology*, 2000, 118(4), A835. http://dx.doi.org/10.1016/S0016-5085(00)85481-5

PMID: 9928283

[98] Kaumann, A.J. Do human atrial 5-HT4 receptors mediate arrhythmias? *Trends Pharmacol. Sci.*, 1994, 15(12), 451-455. http://dx.doi.org/10.1016/0165-6147(94)90058-2

PMID: 7886817

[99] Gershon, M.D. Serotonin is a sword and a shield of the bowel: serotonin plays offense and defense. *Trans. Am. Clin. Climatol. Assoc.*, 2012, 123, 268-280.

PMID: 23303993

[100] Bischoff, S.C.; Mailer, R.; Pabst, O.; Weier, G.; Sedlik, W.; Li, Z.; Chen, J.J.; Murphy, D.L.; Gershon, M.D. Role of serotonin in intestinal inflammation: knockdown of serotonin reuptake transporter exacerbates 2,4,6-trinitrobenzene sulfonic acid colitis in mice. *Am. J. Physiol. Gastrointest. Liver Physiol.*, 2009, 296(3), G685-G695. http://dx.doi.org/10.1152/jappl.90685.2008

PMID: 1905763

[101] Traub, R.J.; Pechman, P.; Iadarola, M.J.; Gebhart, G.F. Fos-like proteins in the lumbosacral spinal cord following noxious and non-noxious colorectal distension in the rat. *Pain*, 1992, 49(3), 393-403. http://dx.doi.org/10.1016/0304-3959(92)90247-9

PMID: 1408305

[102] Bueno, L.; Fioramonti, J. Effects of inflammatory mediators on gut sensitivity. *Can. J. Gastroenterol.*, 1999, 13(Suppl. A), 42A-46A.

http://dx.doi.org/10.1155/1999/846809

PMID: 10202208

[103] Friese, N.; Diop, L.; Chevalier, E.; Angel, F.; Rivière, P.J.; Dahl, S.G. Involvement of prostaglandins and mediators on gut sensitivity. *Gastroenterology*, 2006, 130(5), 1466-1479. http://dx.doi.org/10.1053/j.gastro.2005.11.059

PMID: 16678560

[104] Talley, N.J. Drug treatment of functional dyspepsia. *Scand. J. Gastroenterol. Suppl.*, 1991, 182, 47-60.
[108] Ford, A.C.; Marwaha, A.; Sood, R.; Moayyedi, P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. Gut, 2015, 64(7), 1049-1057. http://dx.doi.org/10.1136/gutjnl-2014-307843 PMID: 25147201

[109] Degen, L.; Petrig, C.; Studer, D.; Schroller, S.; Beglinger, C. Effect of tegaserod on gut transit in male and female subjects. Neurogastroenterol. Motil., 2005, 17(6), 821-826. http://dx.doi.org/10.1111/j.1365-2982.2005.00715.x PMID: 16336497

[110] Mawe, G.M.; Hoffman, J.M. Serotonin signalling in the gut—functions, dysfunctions and therapeutic targets. Nat. Rev. Gastroenterol. Hepatol., 2013, 10(8), 473-486. http://dx.doi.org/10.1038/nrgastro.2013.105 PMID: 23797870

[111] Vakil, N.; Kianifard, F.; Bottoli, I. Exploratory study of tegaserod for dyspepsia in women receiving PPIs for heartburn. Arch. Drug Inf., 2008, 1(3), 79-88. http://dx.doi.org/10.1002/j.1753-5174.2008.00012.x PMID: 19639028

[112] Appel, S.; Kumle, A.; Hubert, M.; Duvauchelle, T. First pharmacokinetic-pharmacodynamic study in humans with a selective 5-hydroxytryptamine4 receptor agonist. J. Clin. Pharmacol., 1997, 37(3), 229-237. http://dx.doi.org/10.1002/j.1552-4604.1997.tb04785.x PMID: 9089425

[113] Merck. Guanidine hydrochloride tablets prescribing information, 2017. Available from: https://www.merck.com/product/usa/pi/circulars/g/guanidine_hydrochloride/guanidine_pi.pdf (Accessed May 17, 2019).

[114] Novartis. Zelnorm (Tegaserod Maleate). Prescribing information, 2007. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/212001.pdf (Accessed May 17, 2019).

[115] Yan, L.J. Reexploring 5-methoxyindole-2-carboxylic acid (MICA) as a potential anti-diabetic agent. Diabetes Metab. Syndr. Obes., 2018, 11, 183-186. http://dx.doi.org/10.2147/DMSO.S166485 PMID: 29765243

[116] Appeal-Dingemanse, S.; Lemarechal, M.O.; Kumle, A.; Hubert, M.; Legangneux, E. Integrated modeling of the clinical pharmacokinetics of SDZ HTF 919, a novel selective 5-HT4 receptor agonist, following oral intravenous administration. J. Clin. Pharmacol., 1999, 47, 483-491. http://dx.doi.org/10.1046/j.1365-2125.1999.00936.x

[117] Appel-Dingemanse, S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT(4) receptor partial agonist with promotile activity. Clin. Pharmacokinet., 2002, 41(13), 1021-1042. http://dx.doi.org/10.2165/00003088-200241130-00002 PMID: 12403641

[118] Tegaserod NDA 21-200. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-200_Zelnorm_biopharmr_P1.pdf (Accessed May 17, 2019) and at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-200_Zelnorm_biopharmr_P2.pdf (Accessed May 17, 2019).

[119] Zhou, H.; Khalilieh, S.; Lau, H.; Guerret, M.; Osborne, S.; Alladina, L.; Laurent, A.L.; McLeod, J.F. Effect of meal timing not critical for the pharmacokinetics of tegaserod (HTF 919). J. Clin. Pharmacol., 1999, 39(9), 911-919. http://dx.doi.org/10.1177/0091270992008524 PMID: 10471981

[120] ZelnormTM (tegaserod maleate) tablets; prescribing information. East Hanover (NJ) Novartis Pharmaceuticals Corporation, 2002 Jul 22; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/212001lbl.pdf (Accessed May 17, 2019).

[121] Appel-Dingemanse, S.; Hirschberg, Y.; Osborne, S.; Pommier, F.; McLeod, J. Multiple-dose pharmacokinetics confirm no accumulation and dose proportionality of the novel promotile drug tegaserod (HTF 919). Eur. J. Clin. Pharmacol., 2001, 56(12), 889-891. http://dx.doi.org/10.1007/s002280000239 PMID: 11317476

[122] Appeal-Dingemanse, S.; Rawls, J.; Heggland, J.; Campestrini, J.; Séchaud, R. Similar pharmacokinetics of tegaserod (HTF 919) in patients with constipation- and diarrhea-predominant irritable bowel syndrome. Gastroenterology, 2000, 118(4), A1160. http://dx.doi.org/10.1016/S0016-5085(00)80460-6

[123] Vickers, A.E.M.; Zollinger, M.; Dannecker, R.; Tynes, R.; Heitz, F.; Fischer, V. In vitro metabolism of tegaserod in human liver and intestine: assessment of drug interactions. Drug Metab. Dispos., 2001, 29(10), 1269-1276. PMID: 11560869

[124] Wagstaff, A.J.; Frampton, J.E.; Croom, K.F. Tegaserod: a review of its use in the management of irritable bowel syndrome with constipation in women. Drugs, 2003, 63(11), 1101-1120. http://dx.doi.org/10.2165/00003495-200363110-00013 PMID: 12749744

[125] Prather, C.M.; Camilleri, M.; Zinsmeister, A.R.; McKinzie, S.; Thomforde, G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology, 2000, 118(3), 463-468. http://dx.doi.org/10.1016/S0016-5085(00)70251-4 PMID: 10702196

[126] Degen, L.; Matzinger, D.; Merz, M.; Appeal-Dingemanse, S.; Osborne, S.; Lüchinger, S.; Bertold, R.; Maecke, H.; Beglinger, C. Tegaserod, a 5-HT4 receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects. Aliment. Pharmacol. Ther., 2001, 15(11), 1745-1751. http://dx.doi.org/10.1046/j.1365-2036.2001.01103.x PMID: 11683688

[127] Degen, L.; Petrig, C.; Studer, D.; Schrroller, S.; Beglinger, C. Effect of tegaserod on gut transit in...
male and female subjects. Neurogastroenterol. Motil., 2005, 17(6), 821-826. http://dx.doi.org/10.1111/j.1365-2982.2005.00715.x PMID: 16336497

[128] Patel, S.; Berrada, D.; Lembo, A. Review of tegaserod in the treatment of irritable bowel syndrome. Expert Opin. Pharmacother., 2004, 5(11), 2369-2379. http://dx.doi.org/10.1517/14656566.5.11.2369 PMID: 15500384

[129] Müller-Lissner, S.; Koch, G.; Talley, N.J.; Drossman, D.; Rueegg, P.; Dunger-Baldauf, C.; Lefkowitz, M. Subject's Global Assessment of Relief: an appropriate method to assess the impact of treatment on irritable bowel syndrome-related symptoms in clinical trials. J. Clin. Epidemiol., 2003, 56(4), 310-316. http://dx.doi.org/10.1016/S0895-4356(03)00027-1 PMID: 12767407

[130] Layer, P.; Keller, J.; Loeffler, H.; Kreiss, A. Tegaserod in the treatment of irritable bowel syndrome (IBS) with constipation as the prime symptom. Ther. Clin. Risk Manag., 2007, 3(1), 107-118. http://dx.doi.org/10.2147/tcrm.2007.3.1.107 PMID: 18360619

[131] Kellow, J.; Chang, O.Y.; Thongsawat, S. Mazlam, M. Tegaserod: long-term treatment for irritable bowel syndrome patients with abdominal pain/discomfort, bloating and constipation: a clinical study. Aliment. Pharmacol. Ther., 2003, 52, 671-676. http://dx.doi.org/10.11136/gut.52.5.671 PMID: 12692051

[132] Chey, W.D. Review article: tegaserod - the global experience. Aliment. Pharmacol. Ther., 2004, 20(Suppl. 7), 15-19. http://dx.doi.org/10.1046/j.1365-2036.2004.02181.x PMID: 15521850

[133] Bardhan, K.D.; Forbes, A.; Marsden, C.L.; Mason, T.; Short, G. The effects of withdrawing tegaserod treatment in comparison with continuous treatment in irritable bowel syndrome patients with abdominal pain/discomfort, bloating and constipation: a clinical study. Aliment. Pharmacol. Ther., 2004, 20(2), 213-222. http://dx.doi.org/10.1111/j.1365-2036.2004.02032.x PMID: 15233702

[134] Nyhlin, H.; Bang, C.; Elsborg, L.; Silvennoinen, J.; Holme, I.; Ruegg, P.; Jones, J.; Wagner, A. A double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. Scand. J. Gastroenterol., 2004, 39(2), 119-126. http://dx.doi.org/10.1080/03655520310006748 PMID: 15000272

[135] Layer, P.; Keller, J.; Mueller-Lissner, S.; Ruegg, P.; Loeffler, H. Tegaserod: long-term treatment for irritable bowel syndrome patients with constipation in primary care. Digestion, 2005, 71(4), 238-244. http://dx.doi.org/10.1159/000087049 PMID: 16024929

[136] Thompson, W.G.; Longstreth, G.F.; Drossman, D.A.; Heaton, K.W.; Irvine, E.J.; Müller-Lissner, S.A. Functional bowel disorders and functional abdominal pain. Gut, 1999, 45(Suppl. 2), II43-II47. http://dx.doi.org/10.1136/gut.45.2008.ii43 PMID: 10457044

[137] Grant Thompson, W. Tegaserod and IBS: a perfect match? Gut, 2003, 52(5), 621-622. http://dx.doi.org/10.1136/gut.52.5.621 PMID: 12692042

[138] Beattie, D.T.; Armstrong, S.R.; Shaw, J.P.; Marquess, D.; Sandlund, C.; Smith, J.A.; Taylor, J.A.; Humphrey, P.P. The in vivo gastrointestinal activity of TD-5108, a selective 5-HT(4) receptor agonist with high intrinsic activity. Naunyn Schmiedebergs Arch. Pharmacol., 2008, 370(1), 139-147. http://dx.doi.org/10.1007/s00210-008-0281-z PMID: 18408918

[139] Seeger, J.D.; Quinn, S.; Earnest, D.L.; Lembo, A.; Kuo, B.; Rivero, E.; Walker, A.M. The Zelnorm epidemiologic study (ZEST): a cohort study evaluating incidence of abdominal and pelvic surgery related to tegaserod treatment. BMC Gastroenterol., 2012, 12, 171. http://dx.doi.org/10.1186/1471-230X-12-171 PMID: 23198861

[140] Drici, M.D.; Ebert, S.N.; Wang, W.X.; Rodriguez, I.; Liu, X.K.; Whitfield, B.H.; Woosley, R.L. Comparison of tegaserod (HTF 919) and its main human metabolite with cisapride and erythromycin on cardiac repolarization in the isolated rabbit heart. J. Cardiovasc. Pharmacol., 1999, 34(1), 82-88. http://dx.doi.org/10.1097/00005344-199907000-00014 PMID: 10413072

[141] Tacik, J.; Camilleri, M.; Chang, L.; Chey, W.D.; Galligan, J.J.; Lacy, B.E.; Müller-Lissner, S.; Quigley, E.M.; Schurkes, J.; De Maeyer, J.H.; Stanton, M.; V. Systematic review: cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. Aliment. Pharmacol. Ther., 2012, 35(7), 745-767. http://dx.doi.org/10.1111/j.1365-2036.2012.05011.x PMID: 22356640

[142] Thompson, C.A. Novartis suspends tegaserod sales at FDA’s request. Am. J. Health Syst. Pharm., 2007, 64(10), 1020. http://dx.doi.org/10.2146/news070044 PMID: 17494895

[143] Anderson, J.L.; May, H.T.; Bair, T.L.; Muhlestein, J.B.; Horne, B.D.; Carlquist, J.F. Lack of association of tegaserod with adverse cardiovascular outcomes in a matched case-control study. J. Cardiovasc. Pharmacol. Ther., 2009, 14(3), 170-175. http://dx.doi.org/10.1177/1074248409340158 PMID: 19602672

[144] Pasricha, P.J. Desperately seeking serotonin. A commentary on the withdrawal of tegaserod and the state of drug development for functional and motility disorders. Gastroenterology, 2007, 132(7), 2287-2290.
Novartis. Press release: Novartis suspends US marketing and sales of Zelnorm in response to request from FDA. Available from: http://hugin.info/134323/R/1116336/204121.pdf (Accessed May 17, 2019).

Sloan Pharma. Briefing Materials, Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committees, 2018. Available from: https://www.fda.gov/media/119013/download (Accessed May 17, 2019).

FDA Briefing Document, Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committees, 2018. Available from: https://www.fda.gov/media/119011/download (Accessed May 17, 2019).

Busti,A.J.; Murillo, J.R.J., Jr; Cryer, B. Tegaserod-induced myocardial infarction: case report and hypothesis. Pharmacotherapy, 2004, 24(4), 526-531. http://dx.doi.org/10.1592/phco.24.5.526.33351 PMID: 15098809

Gomez-Mancilla, B.; Cutler, N.R.; Leibowitz, M.T.; Spierings, E.L.; Klapper, J.A.; Diamond, S.; Goldstein, J.; Smith, T.; Couch, J.R.; Fleishaker, J.; Azie, N.; Blunt, D.E. Safety and efficacy of PNU-142633, a selective 5-HT1D agonist, in patients with acute migraine. Cephalalgia, 2001, 21(7), 727-732. http://dx.doi.org/10.1046/j.1468-2982.2001.00208.x PMID: 11595000

Haenisch, B.; Bönisch, H. Pharmacological characterization of tegaserod at the wild type and 124Cys variant of the human 5-HT1B receptor. Pharmacogenet. Genomics, 2011, 21(7), 432-435. http://dx.doi.org/10.1097/FPC.0b013e3283469f1d PMID: 21478802

Chan, K.Y.; de Vries, R.; Leijten, F.P.; Pfannkuche, H.J.; van den Bogaerd, A.J.; Danser, A.H.; MaassenVanDenBrink, A. Functional characterization of contractions to tegaserod in human isolated proximal and distal coronary arteries. Eur. J. Pharmacol., 2009, 619(1-3), 61-67. http://dx.doi.org/10.1016/j.ejphar.2009.07.010 PMID: 19619527

Serebruany, V.L.; El Mouelhi, M.; Pfannkuche, H.J.; Rose, K.; Marro, M.; Angiolillo, D.J. Investigations on 5-HT4 receptor expression and effects of tegaserod on human platelet aggregation in vitro. Am. J. Ther., 2010, 17(6), 543-552. http://dx.doi.org/10.1097/MJT.0b013e3181b63f21 PMID: 19797939

US Food & Drug Administration. Zelnorm (tegaserod maleate). Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm (Accessed May 17, 2019).

US Food & Drug Administration. Zelnorm (tegaserod maleate) Information. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm (Accessed May 17, 2019).

EMA - Refusal Assessment Report for Zelnorm Procedure No. EMEA/H/C/621. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/000621/WC500058849.pdf (Accessed May 17, 2019).

http://articles.timesofindia.indiatimes.com/2011-03-19/india/29146073_1_dip-blood-sugar-levels-gatifloxacine-tegaserod (Accessed May 17, 2019).