INTRODUCTION

Tegaserod maleate (Zelnorm™, Novartis) is a unique pharmacological agent for the treatment of patients with irritable bowel syndrome (IBS) with constipation (IBS-C). Unlike traditional IBS therapies, which target only single IBS symptoms, tegaserod has provided global relief of the multiple symptoms of IBS, including abdominal pain and discomfort, bloating, and constipation. It has also been found to be safe and well tolerated in both short-term (three-month) and long-term (12-month) clinical trials.

OVERVIEW

IBS is a relatively common gastrointestinal (GI) disorder that affects up to 20% of the U.S. population, with more women affected than men, in a ratio of 2:1. Patients typically first seek medical care between ages 30 and 50 years, although the age of onset is generally younger.

The diagnosis of IBS is made in more than one quarter (28%) of patients who see gastroenterologists. The annual costs associated with the care of these patients in the eight major industrialized countries are approximately $41 billion (in U.S. dollars). The estimated annual total cost of IBS in the U.S., excluding the cost of prescription medications, is $30 billion.

IBS has a substantial negative impact on quality of life. Patients commonly report that symptoms cause them to miss work or school or to be less productive there. Symptoms may also limit patients’ participation in leisure activities and often have an adverse effect on their social and physical relationships. Studies using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), a generic quality-of-life measure, have shown that patients with IBS have poorer quality of life than the general U.S. population, and their scores on selected SF-36 subscales are lower than those of patients with other chronic conditions such as gastroesophageal reflux disease (GERD), asthma, migraine, diabetes mellitus, and end-stage renal disease.

In the clinical setting, the diagnosis of IBS is usually confirmed according to the broad definition of abdominal pain or discomfort associated with altered bowel habits. More detailed symptom-based criteria, the Rome II criteria, are commonly used to identify patients for clinical trials. There are three major subtypes:

- IBS with constipation (IBS-C)
- IBS with diarrhea (IBS-D)
- IBS with alternating diarrhea and constipation (IBS-A)

TRADITIONAL TREATMENT OPTIONS

Until recently, IBS treatment options consisted of single agents—for specific individual symptoms—or various combinations of therapies (e.g., antispasmodics, fiber, laxatives, anti-diarrheal agents, and antidepressants)—targeted at multiple symptoms—in individual patients. However, data to support the efficacy and safety of these therapies in patients with IBS are generally lacking. Furthermore, patient surveys indicate that most patients are dissatisfied with traditional therapies because they are either ineffective or are associated with adverse drug effects (ADEs). Dissatisfaction commonly results in trials of multiple medications, either concurrently or consecutively, or in combination with other medications. Many patients also try alternative remedies when other options fail, although the effectiveness of these therapies is perceived as limited.

The ADEs that are associated with traditional therapies can be particularly troublesome, because they sometimes worsen or mimic IBS symptoms. Antispasmodics and tricyclic antidepressants (TCAs) can cause or exacerbate constipation, fiber may increase symptoms of bloating and abdominal discomfort, anti-diarrheal agents may provoke constipation in some patients, and laxatives may be associated with diarrhea, abdominal discomfort, and gas.

In the IBS Medications Side Effects Study, 35% of survey respondents who had taken over-the-counter laxatives reported that they experienced abdominal discomfort while taking them. Furthermore, bloating was reported by 20% of survey respondents who had taken prescription laxatives, by 26% who had taken nonprescription laxatives, and by 26% who had taken fiber supplements.

Ideally, IBS therapies should provide total relief of abdominal pain or discomfort, bloating, and altered bowel habits. Therapies that do not achieve this goal or that address only individual IBS symptoms should be considered suboptimal. Therapies that provide global relief have greater potential to alleviate symptoms and to improve overall well-being and quality of life. In addition to being effective, IBS treatment options should be safe and well tolerated and should produce a minimal number of ADEs and drug–drug interactions.

PATHOPHYSIOLOGY

Brain–Gut Axis Dysfunction

Symptoms of IBS arise from three main physiological abnormalities: altered GI motility, altered intestinal secretion, and enhanced visceral sensitivity. Although the motor, secretory, and sensory activities of the gut are under the direct control of the enteric nervous system (ENS), the central nervous system (CNS) contributes indirectly by modulating the
activities of the ENS through sympathetic and parasympathetic pathways.\textsuperscript{28,29} This bidirectional communication pathway is referred to as the brain–gut axis. The ENS controls intestinal motility and secretion and visceral sensation via neurotransmitters such as serotonin (5-hydroxytryptamine [5-HT]), norepinephrine, dopamine, acetylcholine, and calcitonin gene-related peptide (CGRP).

The neurotransmitter serotonin is produced and stored primarily in the gut mucosa. Indeed, almost 95% of the body’s 5-HT is made and stored in mucosal enterochromaffin (EC) cells in the GI tract. Serotonin plays a major role in communication between the ENS and its effector systems (Figure 1).\textsuperscript{28,30}

Various 5-HT receptor subtypes exist in the body; those considered to have the largest role in GI regulation are 5-HT\textsubscript{1A}, 5-HT\textsubscript{1D}, 5-HT\textsubscript{2}, 5-HT\textsubscript{3}, and 5-HT\textsubscript{4}. Activation of the 5-HT\textsubscript{3} receptors is associated with increased GI motility and secretion, whereas activation of the 5-HT\textsubscript{4} receptors produces varied excitatory and inhibitory effects,\textsuperscript{28,30} including mediation of the relaxation and contraction of circular smooth muscle strips and induction of small-bowel and colonic fluid secretion.\textsuperscript{30} Serotonin initiates the peristaltic reflex that is mediated by the ENS. Results from in vitro studies from human, rat, and guinea pig intestines suggest that 5-HT\textsubscript{4} receptors are its primary mediators.\textsuperscript{30}

**5-HT Receptor Modulators**

The 5-HT receptor modulator tegaserod was introduced to the U.S. market in July 2002 to treat women with IBS-C and was found to offer comprehensive relief of abdominal discomfort and constipation. Tegaserod is a highly selective 5-HT\textsubscript{4} receptor partial agonist. It is a member of a novel class of compounds, the aminoguanidine indoles, and it is structurally similar to serotonin (Figure 2).\textsuperscript{31,32}

The development of tegaserod began with the structure of serotonin as a starting point, because serotonin is the natural ligand at 5-HT\textsubscript{4} receptors. Tegaserod was then designed according to three principles—selectivity, stability, and polarity. To make tegaserod highly selective, scientists restricted the conformation of the alklyamine side chain. The primary amine was replaced by a basic moiety to give tegaserod greater stability against metabolic degradation. Finally, a relatively high molecular polarity was incorporated so that tegaserod would not cross the blood–brain barrier.\textsuperscript{33}

Tegaserod has 21% affinity for the 5-HT\textsubscript{4} receptor, whereas endogenous 5-HT has 100% affinity.\textsuperscript{34,35} Partial agonists, in comparison with full agonists, are less likely to reduce receptor sensitivity and to produce tachyphylaxis (rapid immunization against the effect of toxic doses or a rapidly decreasing response to a drug after a few doses).\textsuperscript{30,36,37} A lower likelihood of 5-HT\textsubscript{4} receptor desensitization is particularly relevant, because the G-protein–coupled, 7-transmembrane receptor class is especially prone to desensitization that leads to tachyphylaxis or tolerance.\textsuperscript{37} Partial agonists may also have a normalizing effect on endogenous serotonin activity by increasing endogenous activity while decreasing the potential for the exaggerated effects sometimes associated with full agonists.\textsuperscript{36,37}

Tegaserod stimulates the peristaltic reflex and intestinal

![Figure 1](image_url)

Figure 1  The role of serotonin (5-hydroxytryptamine [5-HT]) in gastrointestinal regulation. CNS = central nervous system; ENS = enteric nervous system. (© Novartis Pharmaceuticals Corporation.)
secretion, and it inhibits visceral sensitivity by selectively binding to 5-HT4 receptors.35–38 It amplifies peristaltic reflexes without causing waves of nausea-evoking or pain-producing signals to be sent to the CNS because no 5-HT4 receptors are found on extrinsic sensory nerves.39 The probable presynaptic location of 5-HT4 receptors in the gut also enables tegaserod to increase motility in response to endogenous mucosal stimulation without initiating constitutive, propulsive activity, which tends to cause painful, incapacitating diarrhea if it occurs.39

SAFETY TRIALS

Tegaserod has demonstrated significant beneficial effects in patients (primarily women) with IBS-C. In large, controlled, randomized, phase 3 studies, tegaserod provided significantly greater overall improvement over placebo in relieving multiple and single symptoms of IBS-C, as described next.

Twelve-Week, Double-Blind, Randomized Clinical Trials

Tegaserod was safe and well tolerated in three 12-week, phase 3 clinical trials.2,3,31 In these multicenter, double-blind, placebo-controlled trials, the drug was evaluated at a dose of 6 mg twice daily in a combined total population of 2,632 patients; of these, 93.8% were women.

All patients had at least a three-month history of IBS-C.31 From pooled data, the most common ADEs that occurred more frequently in tegaserod-treated patients than in the placebo patients were headache (15% vs. 12%) and diarrhea (9% vs. 4%) (Table 1).31 Most reported incidences of diarrhea were single episodes that occurred within the first week of therapy and that generally resolved with continued treatment.

Diarrhea caused only 1.6% of patients in the tegaserod group to discontinue therapy.3,31 No reported cases resulted in hospitalization, significant volume depletion, or electrolyte abnormalities.3 Other ADEs that occurred with greater frequency in the tegaserod group than in the placebo group included nausea (8% vs. 7%) and abdominal pain (12% vs. 11%) (see Table 1).31

Twelve-Month Trial

The long-term safety of tegaserod was evaluated in a 12-month, international, multicenter, open-label study of 579 patients (90.3% women) with IBS-C.3 The most commonly reported ADEs that were thought to be possibly related to tegaserod therapy were similar to those reported in three 12-week trials: mild and transient diarrhea (10.1%), headache (8.3%), abdominal pain (7.4%), and flatulence (5.5%) (Table 2). No deaths were reported.

Approximately 11% of patients discontinued therapy because of ADEs; 3.5% withdrew because of diarrhea. As in the 12-week trials, diarrhea was not associated with dehydration or electrolyte imbalances and did not result in any hospitalizations. Approximately 24% of patients in this study had received previous tegaserod therapy. The rates of ADEs were generally similar in this group and in the group new to tegaserod therapy, although abdominal pain was reported more frequently among tegaserod-naive patients (8.1%) than among tegaserod-experienced patients (5.1%)

Ten-Week Study of Patients with Diarrhea

Because the altered bowel function in patients with IBS can change over time, a 10-week, randomized, double-blind, placebo-controlled study was performed to assess the safety of tegaserod in 86 patients (67% were women) with at least a three-month history of IBS-D.6 ADEs were reported in 85.7% of patients receiving 2 mg twice daily, in 82.4% receiving 6 mg twice daily, and in 70.6% receiving placebo. No statistical difference was noted between the tegaserod groups and the placebo group.

With pooling of the data from the two tegaserod-treated groups, the incidence of diarrhea was 33% (vs. 35% in the placebo group; P = not significant), and the incidence of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Adverse Drug Events Occurring in 1% or More Often Than in Placebo Patients in 12-Week Phase 3 Clinical Trials of Tegaserod*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tegaserod 6 mg Twice Daily</strong> (n = 1,327)</td>
<td><strong>Placebo</strong> (n = 1,305)</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
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<tr>
<td>Abdominal pain</td>
<td>12%</td>
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<td>Diarrhea</td>
<td>9%</td>
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<td>Nausea</td>
<td>8%</td>
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<td>Flatulence</td>
<td>6%</td>
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<tr>
<td>Back pain</td>
<td>5%</td>
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<tr>
<td>Dizziness</td>
<td>4%</td>
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<tr>
<td>Accidental trauma</td>
<td>3%</td>
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<tr>
<td>Arthropyathy</td>
<td>2%</td>
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<tr>
<td>Migraine</td>
<td>2%</td>
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<td>Leg pain</td>
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*Values represent combination results from phase three clinical trials; significance was determined only for individual studies.

Data from Zelnorm™ (tegaserod maleate) prescribing information. East Hanover, NJ: Novartis Pharmaceuticals; 2002.31
abdominal pain was 26% (vs. 24% in the placebo group; \( P = \) not significant).

As in studies of patients with IBS-C, diarrhea in this IBS-D patient population was typically mild; 17% of patients receiving tegaserod had severe diarrhea compared with 18% of patients in the placebo group (\( P = \) not significant). Diarrhea also tended to be transient; 71% of cases occurring in patients taking tegaserod 6 mg twice daily and 100% of cases occurring in those taking tegaserod 2 mg twice daily were single episodes, compared with 83% of cases in the placebo group. Eleven patients (13%) in the tegaserod treatment groups discontinued therapy because of ADEs; none of the patients withdrew in the placebo group. Five patients (6%) stopped because of diarrhea and/or abdominal pain.

18-Week Constipation Study

Additional studies have confirmed the safety and tolerability of tegaserod 6 mg twice daily. An 18-week, randomized, double-blind, parallel-group, multicenter study was conducted in the Asia–Pacific region of 520 patients with IBS (88% women) whose primary bowel symptom was not diarrhea. The findings were similar to those reported in phase 3 clinical trials conducted in the U.S.\(^2\text{-}\text{4,31}\)

The most frequently reported ADEs were headache (12.0% vs. 11.1% in the tegaserod and placebo groups, respectively), diarrhea (10.0% vs. 3.1%), and unspecified abdominal pain (5.8% vs. 3.1%). Serious ADEs were infrequent and were less common in the tegaserod group (1.5%) than in the placebo group (3.4%).

More patients in the tegaserod group (7.7%) than in the placebo group (1.5%) discontinued therapy because of ADEs. The ADEs that were most often associated with early discontinuation were diarrhea (2.3% in the tegaserod groups vs. 0% in the placebo group, respectively), abdominal pain (1.5% vs. 0%), nausea (1.2% vs. 0%), and headache (1.2% vs. 0.4%). Rates of withdrawal from the study because of diarrhea in the treated patients were similar to those observed in the phase 3 studies (1.6% in the tegaserod group).

The TENOR Study

The results of the TEGaserod NORdic (TENOR) trial also reinforce the drug’s safety and tolerability profile. In this 12-week, double-blind, placebo-controlled trial, 647 patients (86% women) whose primary bowel symptom was not diarrhea received 6 mg of tegaserod twice daily or placebo.\(^40\) ADEs were more common in the tegaserod group (23.9%) than in the placebo group (13.0%);\(^40\) however, the frequency of serious ADEs was comparable between the tegaserod (1.5%) and the placebo (1.9%) groups.\(^40\)

Diarrhea was the most commonly reported ADE, occurring in 9.2% of the tegaserod patients and in 1.3% of the placebo patients. Eight percent of patients taking tegaserod and 2.5% of patients taking placebo withdrew from the trial as a consequence of ADEs.\(^40\) Diarrhea-related discontinuation rates were 2.8% in the tegaserod group and 0% in the placebo group; these rates were similar to those reported in the phase 3 studies.

Cardiac Effects

The cardiac safety of tegaserod has been closely examined because of reported adverse cardiovascular effects associated with other promotility agents. Tegaserod, an aminoguanidine indole, is structurally distinct from cisapride,\(^7\) which is a substituted piperidyl benzamide (see Figure 2).

At concentrations up to 10 micromoles (\(\mu\)M), tegaserod did not significantly alter the duration of the QT interval in the rabbit heart model;\(^41\) the recommended dose of 6 mg twice daily results in a maximum plasma concentration of 5 nanomoles (nM).\(^7\) Only when the tegaserod concentration was 50 \(\mu\)M (which is approximately 500 to 5,000 times more concentrated than the amount reported in human plasma after doses of up to 100 mg twice daily) were small but significant changes observed in the duration of the QT interval (12±4%; \(P<.05\)).\(^41\)

At concentrations up to 50 \(\mu\)M, the primary metabolite of tegaserod—5-methoxy-indole-3-carboxylic acid glucuronide—had no effect on the length of the QT interval.\(^41\)

Tegaserod 2 mg or 6 mg twice daily was also devoid of clinically relevant electrocardiographic effects in three randomized, double-blind, placebo-controlled, phase 3 clinical trials in 2,516 patients with IBS-C. These studies examined the electrocardiographic safety of tegaserod, with particular focus on the corrected QT (QTc) interval, in patients with and without IBS. The QTc interval is intended to represent the QT interval at a standardized heart rate; because of its inverse relationship to the heart rate, the QT interval is commonly corrected to the heart rate.\(^42\)

A total of 11,535 electrocardiograms from these trials were analyzed.\(^7\) Of the tegaserod-treated patients, 2.3% had pre-existing coronary heart disease and 1.9% had pre-existing
heart-valve disorders. Furthermore, a small number of patients were taking medications with the potential to prolong the QT interval, including class I or III antiarrhythmic agents (0.3% of tegaserod-treated patients), tricyclic antidepressants (5.8%), selective serotonin reuptake inhibitors (SSRIs [9.1%]), and antihistamines (12.6%).

The proportion of patients with a prolonged QTc interval—normal at baseline to prolonged (men, above 450 msec; women, above 470 msec)—during the study and the frequency of overall electrocardiographic abnormalities were the same for the tegaserod patients and the placebo-treated patients. QTc prolongation during the study was observed in 0.4% of patients in the tegaserod group and in 0.6% of those in the placebo group. Abnormal PR and QRS intervals (PR greater than 200 msec; QRS greater than 120 msec) were seen in 2.1% and 0.2% of patients in the tegaserod group and in 2.5% and 0.4% of patients in the placebo group, respectively.

In a separate, placebo-controlled evaluation of 36 healthy men, tegaserod 0.8 to 20 mg administered intravenously did not produce clinically relevant electrocardiographic changes at doses that produced plasma concentrations up to 569 ng/ml (i.e., up to 100 times the levels expected at therapeutic doses).7

Abdominal and Gallbladder Surgery

The U.S. Food and Drug Administration (FDA) initially declined to approve the New Drug Application for tegaserod because of concern that the agent might be associated with a small, statistically insignificant increase in cholecystectomies. Numerous studies have shown that patients with IBS have higher rates of abdominal surgery, including cholecystectomy, than are found in the general population.43–48 The frequency of cholecystectomy reported in the three phase 3, placebo-controlled, 12-week studies was 0.16% (five of 2,965 patients) in the tegaserod group and 0.06% (one of 1,740 patients) in the placebo group (P = .22).49

Several steps were taken to address this concern. First, an expert consensus panel, consisting of 10 gastroenterologists with experience in treating IBS and with clinical pharmacology expertise, reviewed, in a blinded manner, cholecystectomy and abdominal surgery data from the phase 3 clinical trials to assess any potential relationship to tegaserod therapy.49 Three of the five cholecystectomies reported in tegaserod-treated patients were judged to be “definitely” not related to therapy because their symptoms were pre-existing. (One patient had right upper-quadrant pain at the baseline evaluation, and cholelithiasis was discovered only two days after treatment was begun; two patients had symptoms before their entry into the study and had already been scheduled for elective cholecystectomy during the trial.)

The other two cases were considered “probably” not related to tegaserod therapy. A re-analysis, after exclusion of the two cases that were “definitely” not related, revealed similar rates of cholecystectomy among patients taking tegaserod and placebo (two of 2,965 [0.07%] vs. one of 1,740 [0.06%] patients; P = not significant [NS]).49

Similarly, the panel concluded that tegaserod was not associated with an excess number of abdominal or pelvic surgical procedures of any type. In the phase 3 clinical trials, abdominal or pelvic operations were performed in 13 of 2,965 (0.44%) patients who were taking tegaserod and in seven of 1,740 (0.40%) patients taking placebo (P = NS). These included the six patients (described earlier) who had undergone a cholecystectomy. The panel excluded seven more patients (three who were taking tegaserod and four who were taking placebo) because the surgery was either elective or was needed after completion of the double-blind treatment period of the study; therefore, the procedures were deemed “definitely” not related to therapy.

In recalculating the rate of abdominal or pelvic surgery after excluding these 10 patients (three cholecystectomy and seven others), the panel indicated that abdominal and pelvic surgical procedures were performed in seven of 2,965 patients (0.24%) in the tegaserod group and in three of 1,740 patients (0.17%) in the placebo group (P = NS). The panel concluded that the rates of cholecystectomy and other abdominal operations were consistent with expected rates in the total population of women with IBS.

Second, to further determine the potential effects of tegaserod on gallbladder function, investigators observed 12 healthy volunteers and 19 women with IBS-C in a six-week, placebo-controlled, crossover study.50 Tegaserod 6 mg or 12 mg twice daily was administered for two weeks. The researchers measured gallbladder emptying by means of real-time ultrasound and assessed sphincter of Oddi function through ultrasonic measurement of bile duct diameter at three sites. Preliminary findings indicated that neither dose had any effect on the gallbladder or the sphincter of Oddi in healthy people or in women with IBS-C.

Special Patient Populations

The safety and tolerability of medications in special populations (e.g., in elderly patients or patients with renal or hepatic impairment) are always of concern because these conditions are often associated with altered drug metabolism. Although few studies have directly assessed the safety of tegaserod in special populations, several studies have examined potential relationships between age, sex, renal impairment, or hepatic impairment and tegaserod’s pharmacokinetics.31,32,51–54

Age and Sex

Although both men and women were included in phase 3 clinical trials of tegaserod, only 163 men were included in these studies (6.2% of the whole study population); as a result, this number was insufficient to determine the drug’s safety or efficacy in men.31

The pharmacokinetic properties of tegaserod are not influenced by sex.31,32,52 A single, six-week, multcenter, open-label study of tegaserod 6 mg twice daily in 117 patients with IBS-C (of whom 69.2% were men) found that tegaserod was well tolerated and equally effective in relieving abdominal pain and straining in both men and women.31,55

The phase 3 clinical trials included 293 patients aged 65 years or older.31 No differences in safety were observed in the older patients. A study of the agent’s pharmacokinetics, conducted in 40 healthy subjects (10 of each: young men, elderly men, young women, and elderly women), demonstrated that total exposure (area-under-the-plasma concentration time curve extrapolated to infinity [AUC0-∞]) was increased in the

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elderly women (19.2 ± 6.9 ng · hr/ml), compared with young
women (15.7 ± 3.0 ng · hr/ml; P = .002). When the pharma-
cokinetic parameters of tegaserod in all elderly patients were
compared with those in all younger patients, there was no
statistically significant difference in maximum plasma con-
centration (Cmax); however, total exposure remained higher.
The AUC∞,τ was 37% greater ( P < .001), and the AUC0–τ,τ (area
under the plasma concentration time curve from 0 hours to
the time of the last concentration above the limit of quantification)
was 23% greater ( P = .029).32

The degrees of variability in the Cmax and the AUC concentra-
tion observed in this study were similar to those normally
observed in healthy subjects and thus are unlikely to be clin-
cically relevant.36 Tegaserod was safe and well tolerated in all
patients, regardless of age.

In another study of healthy subjects, age did not affect phar-
macokinetic parameters when the patient’s weight was used as
a covariate.31,32

Renal and Hepatic Impairment
Approximately one third of tegaserod (primarily the main
pharmacologically active metabolite, 5-methoxy-indole-3-
carboxylic acid glucuronide) is eliminated by renal excretion.
Even severe renal impairment in which hemo dialysis is nec-
essary (when creatinine clearance is 15 ml/minute per 1.73 m2
or below) does not affect the pharmacokinetics of the parent
drug;31,32,51 however, severe renal impairment does increase
the Cmax by two-fold and the AUC concentration of the main
metabolite by 10-fold.32 The remaining two-thirds of tegaserod
is eliminated unchanged in the feces.

Mild hepatic impairment leads to higher mean AUC (31%
higher) and Cmax (16% higher) values than those observed in
patients with normal hepatic function.31

In patients with mild-to-moderate hepatic impairment (cir-
rhosis, a Child–Pugh clinical assessment score between 5 and
11), administration of single 12-mg oral doses of tegaserod
resulted in statistically insignificant increases in mean
AUC∞,τ (by 43%) and in Cmax (by 18%).32 In this latter study, all
patients with hepatic impairment and 50% of healthy controls
reported mild ADEs, mostly gastrointestinal in nature.

The safety and pharmacokinetic qualities of tegaserod have
not been studied in patients with severe hepatic impairment.

Tegaserod is contraindicated in patients with severe renal
impairment and in those with moderate-to-severe hepatic
impairment;31 however, Swan et al. suggested that the phar-
macokinetic properties of tegaserod were similar in patients
with severe renal insufficiency and in controls.51

Pregnancy
Animal studies have indicated that tegaserod, which is clas-
sified as a pregnancy category B agent,31 does not impair fer-
tility or cause fetal harm at concentrations 15 to 51 times those
expected in humans with recommended doses. However, no
adequate, well-controlled studies in pregnant women have
been undertaken.31 Only limited information has been
obtained from clinical trials during which 15 women with
unintended pregnancies were taking tegaserod and five
women were taking placebo.

Tegaserod is not recommended during pregnancy.32 Its use
in nursing mothers should be carefully evaluated because it is
not known whether this drug is excreted in human milk; how-
ever, it is excreted in the milk of lactating rats at a high milk-
to-plasma ratio.31

DRUG INTERACTIONS
The potential for drug–drug interactions between
tegaserod and concomitantly administered drugs has been
extensively studied in both animal models and humans. To
date, no clinically relevant drug–drug interactions have been
reported.

Orally administered tegaserod is hydrolyzed in the stomach,
and approximately 10% of the drug reaches the bloodstream.37
Once the drug is in the bloodstream, it is 98% protein-bound,
with an estimated steady-state volume of distribution of 388 ±
223 liters.32 Metabolism is accomplished by means of oxidation
and glucuronidation.32 The main metabolite is excreted as N-
glucuronides, mainly in bile, with an estimated terminal half-
life of 11 ± 5 hours.32

Tegaserod is not metabolized by the cytochrome P-450
(CYP-450) enzyme system and has not been found to interact
with it.31 In vitro studies have shown that neither tegaserod nor
its metabolite inhibits CYP-2C8, CYP-2C9, CYP-2C19, CYP-
2E1, or CYP-3A4.31,32 In vivo studies have confirmed the lack
of clinically relevant effects of tegaserod and its metabolite on
the pharmacokinetics of digoxin (tegaserod reduced peak
digoxin levels and total exposure by 15%), oral contraceptives
(tegaserod reduced peak levonorgestrel concentrations by
8%), and warfarin (Coumadin®, Bristol-Myers Squibb).31 Even
though in vitro findings did not rule out inhibition of CYP-2D6
and CYP-1A2 by tegaserod or its metabolite, in vivo studies
with the CYP-2D6 (dextromethorphan) and CYP-1A2 (theo-
phylline) prototypes did not demonstrate any clinically signif-
cant interactions.

Although potential interactions with specific SSRIs have not
been studied, the current evidence suggests that no clinically
relevant interactions occur. Patients participating in tegaserod
clinical trials were allowed to continue taking SSRIs as long as
their doses remained constant for one month before and
during the study; 8.6% of patients received combined tega-
serod–SSRI therapy.37 The safety and efficacy of this combi-
nation were similar to those of tegaserod alone.37

Because SSRIs are metabolized by CYP-2C19, CYP-2D6,
CYP-1A2, and CYP-3A4, tegaserod would not be expected to
influence their metabolism. The SSRIs and their metabolites
are known to influence the activities of a number of these
isoenzymes; however, these effects would not be expected to
influence the metabolism of tegaserod because it is metabo-
lized via entirely separate pathways.

Potential interactions with medications used to treat con-
stipation have not been studied. Fewer than 12% of patients
participating in phase 3 clinical trials were taking fiber or
bulking agents.2 Laxatives were also occasionally used as
rescue medication.2 The use of these agents in these trials did
not appear to influence the safety or efficacy of tegaserod
therapy. The use of other GI motility agents was prohibited in
phase 3 clinical trials, and the effects of concomitant admin-
istration of tegaserod and of other prokinetics have not been
determined.
Tegaserod for Irritable Bowel Syndrome

SUMMARY
Tegaserod is a unique agent that provides global relief of the multiple symptoms of IBS in patients with IBS-C. More than 6,000 patients received tegaserod in short-term (at least eight-week) clinical studies, and many of these patients have remained on therapy for six months (n = 1,200) or 12 months (n = 508). ADEs that were associated with tegaserod in these studies were generally mild and transient in nature. Animal and human studies indicate that tegaserod is not associated with adverse cardiovascular events. A close examination of abdominal surgery data indicates that the use of tegaserod is not associated with increased rates of such procedures. Furthermore, this medication does not appear to alter metabolism significantly, compared with other medications.

Tegaserod has received marketing approval in more than 45 countries. In the U.S., more than 350,000 prescriptions have been filled since the FDA’s approval in July 2002. Post-marketing safety assessments are being conducted.

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