### 8.1 Pregnancy

In animal reproduction studies, decreased survival of rat pups was observed with maternal dietary administration of tegaserod at 71 times the recommended human dose, but there were no findings consistent with maternal toxicity. In a study in rabbits, no evidence of toxicity was observed at up to three times the recommended human dose.

Carcinogenicity studies have not been performed.

There were no effects on fertility in rats treated with tegaserod at doses up to 15 times the recommended human dose.

The ability of tegaserod to penetrate human breast milk has not been determined. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, breastfeeding is not recommended during treatment with ZELNORM.

### 6.2 Postmarketing Experience

Given the known association of tegaserod with increased risk of ischemic colitis and other forms of intestinal ischemia, ZELNORM should be used only in patients in whom the benefit outweighs the risk.

Gastrointestinal motility disorders, the frequency of suicidal ideation/behavior with tegaserod treatment (8 events/10,003, or 0.08%) was higher than placebo (1 event/5,425, or 0.02%).

Two ZELNORM-treated patients committed suicide, one in a controlled study of IBS-C and one during open label treatment for another motility disorder. In 27 placebo-treated and 52 tegaserod-treated patients who committed suicide or made suicide attempts, there were no sex or age differences (12 females, 20 males, 40 patients under 65, 17 patients 65 years or older). Suicide attempt rates in these populations were not statistically different from prior reports in the general population.

### Adverse Reactions

#### Common Adverse Reactions

- Asthenia
- Nausea
- Headache
- Abdominal pain
- Diarrhea
- Constipation
- Flatulence
- Eructation
- Vomiting
- Tiredness
- Dizziness
- Dry mouth
- Insomnia
- Headache

#### Less Common Adverse Reactions

- Volume Depletion Associated with Diarrhea: Avoid use in patients with severe diarrhea.
- Ischemic Colitis: This condition is rare but serious. It can be life-threatening and is often accompanied by abdominal pain, cramping, and blood in the stool. If you experience any symptoms suggestive of ischemic colitis, stop taking ZELNORM and seek medical attention immediately.
- Volume Depletion: These reactions can be serious and may require medical intervention.

### Investigational Studies

A retrospective analysis of the pooled clinical trial database data (involving 18,645 patients, both male and female) of 29 placebo-controlled trials of IBS-C and other motility disorders was conducted to determine 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). All events occurred in male and female patients with a history of cardiovascular disease and were considered to be not clinically meaningful.

### Table: Adverse Events Observed in ≥ 5% of Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>ZELNORM</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Constipation</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### Investigations

- Gastrointestinal Disorders:
  - Abdominal pain
  - Upper abdominal pain
  - Lower abdominal pain
  - Abdominal discomfort
  - Abdominal tenderness
  - Epigastric pain or discomfort

- Migraine

### Limitations of Use

- Patients with a history of ischemic colitis or other forms of intestinal ischemia (4, 5.2)
- Patients with cardiovascular disease (4)
- Patients with severe diarrhea (5.3)
- Patients in whom the benefit outweighs the risk (8.1)

### Dosage and Administration

**ZELNORM Tablets:**

- **DOSAGE FORMS AND STRENGTHS:** Tablets: 6 mg tegaserod.
- **INDICATIONS AND USAGE:** ZELNORM is a 5-HT4 receptor agonist indicated for the treatment of adult women less than 65 years of age with IBS-C. It is not recommended for male patients with this indication.
- **CONTRAINDICATIONS:** ZELNORM is contraindicated in patients with severe diarrhea, history of ischemic colitis or other forms of intestinal ischemia, history of cardiovascular ischemic disease, severe hepatic or renal impairment, or history of serotonin syndrome.
- **WARNINGS AND PRECAUTIONS:** ZELNORM may cause ischemic colitis and other forms of intestinal ischemia. It is recommended to be used only in patients in whom the benefit outweighs the risk.

### Table: Adverse Event

<table>
<thead>
<tr>
<th>Event</th>
<th>ZELNORM</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Flatulence</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### Pharmacokinetics

Compared to under fasted conditions, the tegaserod AUC was reduced by 40% to 65%, Cmax was reduced by approximately 20% to 40% and median Tmax was 0.7 hours. The tegaserod AUC is not considered to be clinically meaningful.

### Clinical Pharmacology

- Following oral administration, tegaserod and its metabolites are excreted in the milk of lactating rats with a milk to plasma concentration ratio of 33:1 at eight hours. Therefore, breastfeeding is not recommended during treatment with ZELNORM.
- The following is a list of less common adverse reactions reported in ≤ 2% of patients in clinical trials of IBS-C on ZELNORM but more frequently than placebo:
  - Abdominal pain
  - Upper abdominal pain
  - Lower abdominal pain
  - Abdominal discomfort
  - Abdominal tenderness
  - Epigastric pain or discomfort
  - Volume Depletion
  - Dizziness

### Reference

- [Tegaserod Faqs](#)
In two randomized, placebo-controlled, double-blind trials enrolling 288 males, efficacy response rates were similar between ZELNORM and placebo in the male subgroup as at least a 1-point reduction in the scale. During the first four weeks in the fixed dose trials, 8% to 11% more ZELNORM-treated patients than placebo-treated patients were responders for abdominal pain/discomfort. Similarly, 9% to 12% more ZELNORM-treated patients were responders for bloating. Corresponding differences at month 3 were as at least a 1-point reduction in the scale. In addition, individual symptoms of abdominal pain/discomfort and bloating were assessed daily using a six or seven point intensity scale. A positive response was defined as at least two of the four weeks, or if they were at least somewhat relieved for each of the four weeks.

### Table 3. Efficacy Responder* Rates in the Three Placebo-Controlled IBS-C Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Placebo</th>
<th>ZELNORM</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>116/752 (20%)</td>
<td>142/752 (29%)</td>
<td>0%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Study 2</td>
<td>76/244 (31%)</td>
<td>97/244 (40%)</td>
<td>0%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Study 3</td>
<td>128/496 (52%)</td>
<td>151/496 (57%)</td>
<td>0%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Responder rate was defined as at least a 1-point reduction in the severity of abdominal pain/discomfort and bloating scales.

**Month 3 results are based on a significant proportion of patients remaining on the same dose regimen of tegaserod 6 mg twice daily while Study 3 utilized a dose-titration design.

---

**Administration Information**

Instruct patients, caregivers, and families that if any of these symptoms occur, they should immediately discontinue ZELNORM and report behaviors of concern to their healthcare provider.

**Suicidal Ideation and Behavior**

[see Warnings and Precautions (5.3)]

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**Medication Guide for ZELNORM**

**ZELNORM**

**PROPOSED INDICATION**

ZELNORM is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adult patients with a history of abdominal pain and at least two of the following symptoms: bloating, cramping, and/or diarrhea.

**INDICATIONS AND USAGE**

ZELNORM is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adult patients with a history of abdominal pain and at least two of the following symptoms: bloating, cramping, and/or diarrhea.

**CONTRAINDICATIONS**

ZELNORM is contraindicated in patients with a history of diverticular disease.

**PRECAUTIONS**

**Suicidal Ideation and Behavior**

Suicidal ideation and behavior (suicidality) have been observed with antidepressant drugs and with ZELNORM. Sudden discontinuation of ZELNORM may lead to symptoms of depression, unusual changes in mood or behavior, begin to have suicidal thoughts or behavior, or thoughts of self-harm.

**Drug Interactions**

ZELNORM is a CYP3A4 and CYP2B6 inhibitor. It should not be coadministered with theophylline (CYP1A2 substrate), dextromethorphan (CYP2D6 substrate), digoxin (P-gp substrate), warfarin (CYP2C9 substrate), or oral contraceptives (ethynyl estradiol monohydrate and norethindrone acetate, a CYP3A4 substrate).

**Adverse Reactions**

The most common adverse reactions of ZELNORM are: nausea, dizziness, stomach-area (abdominal) pain, indigestion, headache, gas, diarrhea, cramping, flatulence, heartburn, belching, headache, constipation, rectal area pain, and visual changes.

**References**

For more information, call 1-855-697-9232.

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