5.3 Volume Depletion Associated with Diarrhea

ZELNORM is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) [see Contraindications (4)]

3 DOSAGE FORMS AND STRENGTHS

Table 2. Number of MACE Events Confirmed in Two External Adjudications of the Clinical Trial Database

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events Confirmed</th>
<th>% of Events Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td>0.00%</td>
</tr>
<tr>
<td>ZELNORM</td>
<td>18</td>
<td>0.01%</td>
</tr>
</tbody>
</table>

8.1 Pregnancy

The milk to plasma concentration ratio for tegaserod is very high. Tegaserod is present in rat milk; the survival rate through postnatal days 4 and 21 was 59% at 300 mg/kg/day as compared to 95% to 99% in the control placebo-treated group.

Gastrointestinal Motility Disorders

Suicidal Ideation/Behavior

In postmarketing experience, serious consequences of diarrhea including hypovolemia, hypotension, and syncope have been reported in patients treated with ZELNORM. In patients whose diarrhea was severe or severe enough to lead to volume depletion, ZELNORM was usually discontinued.

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 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%). Events on ZELNORM included one completed suicide, two suicide attempts, four cases of self-injurious behavior, and one case of suicidal ideation. There was no higher frequency of suicidal ideation/behavior with tegaserod treatment than placebo in patients with irritable bowel syndrome with constipation only, but the frequency of suicidal ideation/behavior with tegaserod treatment was higher in patients with irritable bowel syndrome with diarrhea.

Gastrointestinal hemorrhage was not considered to be related to ZELNORM treatment by investigators in the clinical trials. However, in pooled clinical trials of IBS-C, a retrospective analysis revealed that the frequency of rectal hemorrhage in patients treated with ZELNORM was higher compared to placebo.

There is a lack of adequate and well-controlled studies with ZELNORM in children less than 18 years of age. ZELNORM is not approved for intravenous administration.

8.7 Pregnancy

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unscheduled DNA synthesis (UDS) test or the inhibition of the hERG (human Ether-a-go-go-Related Gene) channel was evident only in the micromolar concentration range with an IC50 of 13 micromolar (approximately 83 to 110 times the recommended dose based on AUC). There was no evidence of carcinogenicity at lower doses (3 to 35 times the recommended dose based on AUC).

The same efficacy variable (i.e., complete relief, considerable relief, somewhat relief, unchanged, worse) was analyzed on a weekly basis. The proportion of all female patients indicated a potential inhibition of MATE1, MATE2-K, and BCRP by tegaserod at high concentrations. However, at the clinical dose of ZELNORM, a significant interaction via inhibition of these transporters is unlikely.

Limited induction of CYP1A2 was observed at tegaserod concentrations in excess of 100 times the clinically relevant range. Coadministration of ZELNORM 6 mg twice daily with warfarin for seven days did not significantly alter the pharmacokinetics of either R- or S-warfarin or change the international normalized ratio (INR) in a group of healthy volunteers. Furthermore, tegaserod administration at a single dose of 6 mg twice daily on day 21 did not significantly affect 

In a pharmacodynamic study of formulation in 10 men, serum ethinyl estradiol concentration was increased by 11% and 18% respectively, compared to ZELNORM administered alone. This change in exposure is not considered clinically relevant.

Advising a woman that breastfeeding is not recommended during treatment with ZELNORM is indicated (see Warnings and Precautions (5.4)).

Omeprazole:

Administration of a single dose of digoxin following ZELNORM 6 mg twice daily for 4 days reduced the mean Cmax and AUC of digoxin by approximately 15%. This change in exposure is not considered clinically relevant.

Administration of omeprazole 20 mg once daily for four days followed by ZELNORM 6 mg twice daily on day four increased the mean tegaserod AUC and Cmax by 15% and 17%, respectively, compared to ZELNORM administered alone. This increase in exposure is not considered clinically relevant.

In chronic toxicology studies in rats and dogs, there were no treatment-related changes in cardiac morphology after tegaserod administration at doses up to 100 times the IC50.

The effect of tegaserod on the QT interval of the electrocardiogram (ECG) was studied in 56 healthy male volunteers given single oral doses of 0.1 mg, 1 mg, and 10 mg (20% of the recommended dose, 200% of the recommended dose, and 2000% of the recommended dose). The highest dose produced a small increase in the QT interval of 9-10 msec, which was not considered clinically relevant.

Although tegaserod is expected to bind to 5-HT2B receptors in humans at the recommended dose, there does not appear to be any potential for heart valve injury based on data from toxicology studies.

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