



## Zelnorm<sup>®</sup> (tegaserod maleate)

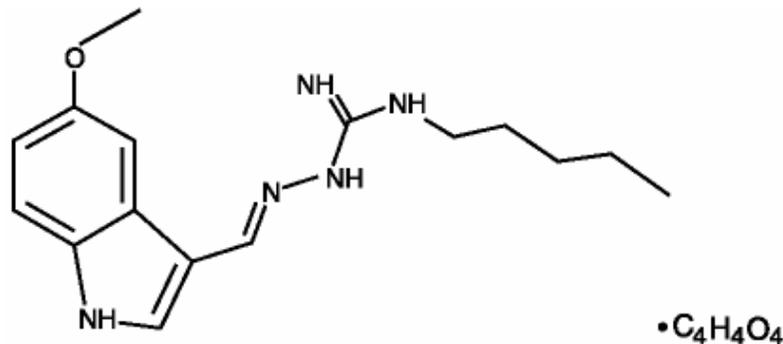
Tablets

Rx only

### Prescribing Information

#### DESCRIPTION

Zelnorm<sup>®</sup> (tegaserod maleate) tablets contain tegaserod as the hydrogen maleate salt. As the maleate salt, tegaserod is chemically designated as 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate. Its empirical formula is  $C_{16}H_{23}N_5O \cdot C_4H_4O_4$ . The molecular weight is 417.47 and the structural formula is



Tegaserod as the maleate salt is a white to off-white crystalline powder and is slightly soluble in ethanol and very slightly soluble in water. Each 1.385 mg of tegaserod as the maleate is equivalent to 1 mg of tegaserod. Zelnorm is available for oral use as tablets containing either 2 mg or 6 mg of tegaserod; inactive ingredients are crospovidone, glyceryl monostearate, hypromellose, lactose monohydrate, poloxamer 188, and polyethylene glycol 4000.

#### CLINICAL PHARMACOLOGY

##### Mechanism of Action

Clinical investigations have shown that both motor and sensory functions of the gut appear to be altered in patients suffering from irritable bowel syndrome (IBS). Both the enteric nervous system, which acts to integrate and process information in the gut, and 5-hydroxytryptamine (5-HT, serotonin) are thought to represent key elements in the etiology of IBS. Approximately 95% of serotonin is found throughout the gastrointestinal tract, primarily stored in enterochromaffin cells but also in enteric nerves acting as a neurotransmitter. Serotonin has been shown to be involved in regulating motility, visceral sensitivity and

intestinal secretion. Investigations suggest an important role of serotonin Type-4 (5-HT<sub>4</sub>) receptors in the maintenance of gastrointestinal functions in humans.

Tegaserod is a 5-HT<sub>4</sub> receptor partial agonist that binds with high affinity at human 5-HT<sub>4</sub> receptors, whereas it has no appreciable affinity for 5-HT<sub>3</sub> or dopamine receptors. It has moderate affinity for 5-HT<sub>1</sub> receptors. Tegaserod, by acting as an agonist at neuronal 5-HT<sub>4</sub> receptors, triggers the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. The activation of 5-HT<sub>4</sub> receptors in the gastrointestinal tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity. In vivo studies showed that tegaserod enhanced basal motor activity and normalized impaired motility throughout the gastrointestinal tract. In addition, studies demonstrated that tegaserod moderated visceral sensitivity during colorectal distension in animals.

## **Pharmacokinetics**

### ***Absorption***

Peak plasma concentrations are reached approximately 1 hour after oral dosing. The absolute bioavailability of tegaserod when administered to fasting subjects is approximately 10%. The pharmacokinetics are dose proportional over the 2 mg to 12 mg range given twice daily for 5 days. There was no clinically relevant accumulation of tegaserod in plasma when a 6 mg b.i.d. dose was given for 5 days. (See DOSAGE AND ADMINISTRATION.)

### ***Food Effects***

When the drug is administered with food, the bioavailability of tegaserod is reduced by 40%-65% and C<sub>max</sub> by approximately 20%-40%. Similar reductions in plasma concentration occur when tegaserod is administered to subjects within 30 minutes prior to a meal, or 2.5 hours after a meal. T<sub>max</sub> of tegaserod is prolonged from approximately 1 hour to 2 hours when taken following a meal, but decreased to 0.7 hours when taken 30 minutes prior to a meal.

### ***Distribution***

Tegaserod is approximately 98% bound to plasma proteins, predominantly alpha-1-acid glycoprotein. Tegaserod exhibits pronounced distribution into tissues following intravenous dosing with a volume of distribution at steady-state of 368 ± 223 L.

### ***Metabolism***

Tegaserod is metabolized mainly via two pathways. The first is a presystemic acid catalyzed hydrolysis in the stomach followed by oxidation and conjugation which produces the main metabolite of tegaserod, 5-methoxyindole-3-carboxylic acid glucuronide. The main metabolite has negligible affinity for 5HT<sub>4</sub> receptors in vitro. In humans, systemic exposure to tegaserod was not altered at neutral gastric pH values. The second metabolic pathway of tegaserod is direct glucuronidation which leads to generation of three isomeric N-glucuronides.

### ***Elimination***

The plasma clearance of tegaserod is 77 ± 15 L/h with an estimated terminal half-life (T<sub>1/2</sub>) of 11 ± 5 hours following intravenous dosing. Approximately two-thirds of the orally administered dose of tegaserod is excreted unchanged in the feces, with the remaining one-third excreted in the urine, primarily as the main metabolite.

## Sub Populations

**Patients:** The pharmacokinetics of tegaserod in IBS patients are comparable to those in healthy subjects.

**Reduced Renal Function:** No change in the pharmacokinetics of tegaserod was observed in subjects with severe renal impairment requiring hemodialysis (creatinine clearance  $\leq 15\text{mL}/\text{min}/1.73\text{m}^2$ ).  $C_{\text{max}}$  and AUC of the main pharmacologically inactive metabolite of tegaserod, 5-methoxy-indole-3-carboxylic acid glucuronide, increased 2- and 10-fold respectively, in subjects with severe renal impairment compared to healthy controls. No dosage adjustment is required in patients with mild-to-moderate renal impairment. Tegaserod is not recommended in patients with severe renal impairment.

**Reduced Hepatic Function:** In subjects with mild hepatic impairment, mean AUC was 31% higher and  $C_{\text{max}}$  16% higher compared to subjects with normal hepatic function. No dosage adjustment is required in patients with mild impairment, however, caution is recommended when using tegaserod in this patient population. Tegaserod has not adequately been studied in patients with moderate and severe hepatic impairment, and is therefore not recommended in these patients.

**Gender:** Gender has no effect on the pharmacokinetics of tegaserod.

**Race:** Data were inadequate to assess the effect of race on the pharmacokinetics of tegaserod.

**Age:** In a clinical pharmacology study conducted to assess the pharmacokinetics of tegaserod administered to healthy young (18-40 years) and healthy elderly (65-85 years) subjects, peak plasma concentration and exposure were 22% and 40% greater, respectively, in elderly females than young females but still within the variability seen in tegaserod pharmacokinetics in healthy subjects. Based on an analysis across several pharmacokinetic studies in healthy subjects, there is no age effect on the pharmacokinetics of tegaserod when allowing for body weight as a covariate. Therefore, dose adjustment in elderly patients is not necessary.

## CLINICAL STUDIES

In three multicenter, double-blind, placebo-controlled studies, 2,470 women (mean age 43 years [range 17-89 years]; 86% Caucasian, 10% African American) with at least a 3-month history of IBS symptoms prior to the study baseline period that included abdominal pain, bloating and constipation received either Zelnorm<sup>®</sup> (tegaserod maleate) 6 mg b.i.d. or placebo. In all patients, constipation was characterized by at least two of the following three symptoms each occurring  $\geq 25\%$  of the time over a 3-month period:  $< 3$  bowel movements/week, hard or lumpy stools, or straining with a bowel movement. Study design consisted of a 4-week placebo-free baseline period followed by a 12-week double-blind treatment period. Study 1 and 2 evaluated a fixed dose regimen of tegaserod 6 mg b.i.d. while Study 3 utilized a dose-titration design.

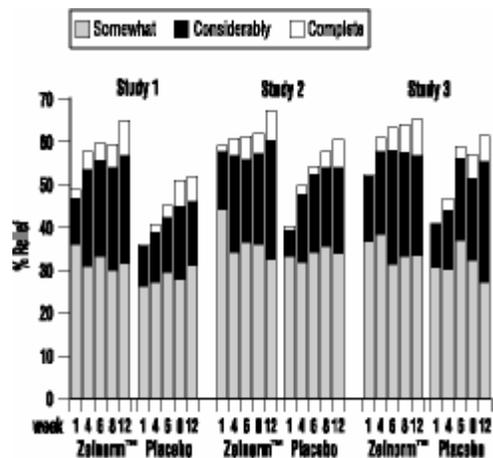
Each week of the 4-week placebo-free baseline period and the 12-week double-blind treatment period, patients were asked the question, "Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?" The response variable consisted of the following 5 categories: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Patients were classified as responders within a month if they were considerably or completely relieved for at least two of the four weeks, or if they were at least somewhat relieved for each of the four weeks.

Calculated response rates during month 1 and during month 3 as described above are shown in the table below. The differences in response rates vs. placebo were greater at month 1 than month 3.

Study	Month 1			Month 3		
	Zelnorm <sup>®</sup> 6 mg b.i.d.	Placebo	Difference (95% Confidence Interval)	Zelnorm <sup>®</sup> 6 mg b.i.d.	Placebo	Difference (95% Confidence Interval)
1	76/244 (31%)	42/240 (17%)	14% (6% to 21%)	95/244 (39%)	66/240 (28%)	11% (3% to 20%)
2	265/767 (35%)	164/752 (22%)	13% (8% to 17%)	334/767 (44%)	292/752 (39%)	5% (0% to 10%)
3	80/233 (34%)	47/234 (20%)	14% (6% to 22%)	100/233 (43%)	88/234 (38%)	5% (-4% to 14%)

Response:  $\geq 2$  of 4 weeks complete or considerable relief or 4 of 4 weeks with at least somewhat relief.

The same efficacy variable (i.e., complete relief, considerable relief, somewhat relief, unchanged, worse) was analyzed on a weekly basis. The proportion of patients with complete, considerable or somewhat relief at weeks 1, 4, 6, 8 and 12 are shown in the figure below.



In addition, individual symptoms of abdominal pain/discomfort and bloating were assessed daily using a 6 or 7 point intensity scale. A positive response was defined as at least a 1 point reduction in the scale. During the first four weeks in the fixed dose studies, 8 to 11% more Zelnorm-treated patients than placebo 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 1 to 10% for abdominal pain/discomfort and 4 to 11% for bloating. Patients on Zelnorm also experienced an increase in median number of stools from 3.8/week at baseline to 6.3/week at month 1 and 6.0/week at month 3, while placebo patients increased from 4.0/week to 5.1/week at month 1 and 5.5/week at month 3.

The efficacy of Zelnorm beyond 12 weeks has not been studied.

## INDICATIONS AND USAGE

Zelnorm<sup>®</sup> (tegaserod maleate) is indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation.

The safety and effectiveness of Zelnorm in men have not been established.

## CONTRAINDICATIONS

Zelnorm<sup>®</sup> (tegaserod maleate) is contraindicated in those patients with:

- severe renal impairment
- moderate or severe hepatic impairment
- a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions
- a known hypersensitivity to the drug or any of its excipients

## WARNINGS

Serious consequences of diarrhea, including hypovolemia, hypotension, and syncope have been reported in the clinical studies and during marketed use of Zelnorm. In some cases, these complications have required hospitalization for rehydration. Zelnorm should be discontinued immediately in patients who develop hypotension or syncope. Zelnorm should not be initiated in patients who are currently experiencing or frequently experience diarrhea (see ADVERSE REACTIONS).

## PRECAUTIONS

### General

Zelnorm should be discontinued immediately in patients with new or sudden worsening of abdominal pain.

### Ischemic colitis

Ischemic colitis and other forms of intestinal ischemia have been reported in patients receiving Zelnorm during marketed use of the drug (see ADVERSE REACTIONS: Post-Marketing Experience). A causal relationship between Zelnorm use and these events has not been established. Placebo-controlled clinical trials of 7,000 patients for 3-month duration showed no cases of these events and would suggest the rate of these events is low. Zelnorm should be discontinued immediately in patients who develop symptoms of ischemic colitis, such as rectal bleeding, bloody diarrhea or new or worsening abdominal pain. Patients developing these symptoms should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with Zelnorm should not be resumed in patients who develop findings consistent with ischemic colitis.

### Information for Patients

Patients should take Zelnorm before a meal.

Patients should stop Zelnorm treatment and consult their physician if they experience new or worsening abdominal pain with or without rectal bleeding.

Patients should also be aware of the possible occurrence of diarrhea during therapy. The majority of the Zelnorm patients reporting diarrhea had a single episode. In most cases, diarrhea occurred within the first week of treatment. Typically, diarrhea resolved with continued therapy. Patients should consult their physician if they experience severe diarrhea, or if the diarrhea is accompanied by severe cramping, abdominal pain, or dizziness. Patients should not initiate therapy with Zelnorm if they are currently experiencing or frequently experience diarrhea. (See ADVERSE REACTIONS.)

## Drug Interactions

In vitro drug-drug interaction data with tegaserod indicated no inhibition of the cytochrome P450 isoenzymes CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4, whereas inhibition of CYP1A2 and CYP2D6 could not be excluded. However, in vivo, no clinically relevant drug-drug interactions have been observed with dextromethorphan (CYP2D6 prototype substrate), and theophylline (CYP1A2 prototype substrate). There was no effect on the pharmacokinetics of digoxin, oral contraceptives, and warfarin. The main human metabolite of tegaserod hydrogen maleate, 5-methoxyindole-3-carboxylic acid glucuronide, did not inhibit the activity of any of the above cytochrome P450 isoenzymes in in vitro tests.

**Dextromethorphan:** A pharmacokinetic interaction study demonstrated that co-administration of tegaserod and dextromethorphan did not change the pharmacokinetics of either compound to a clinically relevant extent. Dose adjustment of either drug is not necessary when tegaserod is combined with dextromethorphan. Therefore, tegaserod is not expected to alter the pharmacokinetics of drugs metabolized by CYP2D6 (e.g., fluoxetine, omeprazole, captopril).

**Theophylline:** A pharmacokinetic interaction study demonstrated that co-administration of tegaserod and theophylline did not affect the pharmacokinetics of theophylline. Dose adjustment of theophylline is not necessary when tegaserod is co-administered. Therefore, tegaserod is not expected to alter the pharmacokinetics of drugs metabolized by CYP1A2 (e.g., estradiol, omeprazole).

**Digoxin:** A pharmacokinetic interaction study with digoxin demonstrated that concomitant administration of tegaserod reduced peak plasma concentration and exposure of digoxin by approximately 15%. This reduction of bioavailability is not considered clinically relevant. When tegaserod is co-administered with digoxin dose adjustment is unlikely to be required.

**Warfarin:** A pharmacokinetic and pharmacodynamic interaction study with warfarin demonstrated no effect of concomitant administration of tegaserod on warfarin pharmacokinetics and pharmacodynamics. Dose adjustment of warfarin is not necessary when tegaserod is co-administered.

**Oral Contraceptives:** Co-administration of tegaserod did not affect the steady-state pharmacokinetics of ethinylestradiol and reduced peak concentrations and exposure of levonorgestrel by 8%. Tegaserod is not expected to alter the risk of ovulation in subjects taking oral contraceptives. No alteration in oral contraceptive medication is necessary when tegaserod is co-administered.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

Tegaserod was not carcinogenic in rats given oral dietary doses up to 180 mg/kg/day (approximately 93 to 111 times the human exposure at 6 mg b.i.d. based on plasma  $AUC_{0-24 \text{ hr}}$ ) for 110 to 124 weeks.

In mice, dietary administration of tegaserod for 104 weeks produced mucosal hyperplasia and adenocarcinoma of small intestine at 600 mg/kg/day (approximately 83 to 110 times the human exposure at 6 mg b.i.d. based on plasma  $AUC_{0-24 \text{ hr}}$ ). There was no evidence of carcinogenicity at a lower dose of 200 mg/kg/day (approximately 24 to 35 times the human exposure at 6 mg b.i.d. based on plasma  $AUC_{0-24 \text{ hr}}$ ) or 60 mg/kg/day (approximately 3 to 4 times the human exposure at 6 mg b.i.d. based on plasma  $AUC_{0-24 \text{ hr}}$ ).

Tegaserod was not genotoxic in the in vitro Chinese hamster lung fibroblast (CHL/V79) cell chromosomal aberration test, the in vitro Chinese hamster lung fibroblast (CHL/V79) cell forward mutation test, the in vitro rat hepatocyte unscheduled DNA synthesis (UDS) test or the in vivo mouse micronucleus test. The results of Ames test for mutagenicity were equivocal.

Tegaserod at oral doses up to 240 mg/kg/day (approximately 57 times the human exposure at 6 mg b.i.d. based on plasma AUC<sub>0-24 hr</sub>) in male rats and 150 mg/kg/day (approximately 42 times the human exposure at 6 mg b.i.d. based on plasma AUC<sub>0-24 hr</sub>) in female rats was found to have no effect on fertility and reproductive performance.

### **Pregnancy, Teratogenic Effects: Pregnancy Category B**

Reproduction studies have been performed in rats at oral doses up to 100 mg/kg/day (approximately 15 times the human exposure at 6 mg b.i.d. based on plasma AUC<sub>0-24 hr</sub>) and rabbits at oral doses up to 120 mg/kg/day (approximately 51 times the human exposure at 6 mg b.i.d. based on plasma AUC<sub>0-24 hr</sub>) and have revealed no evidence of impaired fertility or harm to the fetus due to tegaserod. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### **Nursing Mothers**

Tegaserod and its metabolites are excreted in the milk of lactating rats with a high milk to plasma ratio. It is not known whether tegaserod is excreted in human milk. Many drugs, which are excreted in human milk, have potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for tegaserod in the mouse carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **Pediatric Use**

The safety and effectiveness of Zelnorm in pediatric patients below the age of 18 have not been established.

### **Geriatric Use**

Of 4,035 patients in Phase 3 clinical studies of Zelnorm, 290 were at least 65 years of age, while 52 were at least 75 years old. No overall differences in safety was observed between these patients and younger patients with regard to adverse events.

A clinical study conducted to assess the pharmacokinetics of tegaserod in healthy young (18-40 years) versus healthy elderly (65-85 years) subjects did not indicate that a dose adjustment is necessary when administering Zelnorm to patients over 65 years old. (See CLINICAL PHARMACOLOGY.)

## **ADVERSE REACTIONS**

In Phase 3 clinical trials in which 2,632 patients received Zelnorm<sup>®</sup> (tegaserod maleate) 6 mg b.i.d. or placebo, the following adverse experiences were reported in 1% or more of patients who received Zelnorm and occurred more frequently on Zelnorm than placebo:

**Adverse Events Occurring in ≥ 1% of IBS Patients and More Frequently on  
Zelnorm<sup>®</sup> (tegaserod maleate) than Placebo**

<b>System/ Adverse Experience</b>	<b>Zelnorm<sup>®</sup> 6 mg b.i.d. (n=1,327)</b>	<b>Placebo (n=1,305)</b>
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***Gastrointestinal System Disorders***

Abdominal Pain	12%	11%
Diarrhea	9%	4%
Nausea	8%	7%
Flatulence	6%	5%
<b>Central and Peripheral Nervous System</b>		
Headache	15%	12%
Dizziness	4%	3%
Migraine	2%	1%
<b>Body as a Whole - General Disorders</b>		
Accidental Trauma	3%	2%
Leg Pain	1%	< 1%
<b>Musculoskeletal System Disorders</b>		
Back Pain	5%	4%
Arthropathy	2%	1%

Zelnorm was not associated with changes in ECG intervals.

The following adverse events also occurred during treatment with Zelnorm.

### Zelnorm-Induced Diarrhea

In the Phase 3 clinical studies, 8.8% of patients receiving Zelnorm reported diarrhea as an adverse experience compared to 3.8% of patients receiving placebo. The majority of the Zelnorm patients reporting diarrhea had a single episode. In most cases, diarrhea occurred within the first week of treatment. Typically, diarrhea resolved with continued therapy. Overall, the discontinuation rate from the studies due to diarrhea was 1.6% among the Zelnorm-treated patients. In clinical studies, a small number of patients (0.04%) experienced clinically significant diarrhea including hospitalization, hypovolemia, hypotension and need for intra-venous fluids. Patients who experience severe diarrhea during therapy with Zelnorm should be directed to consult their physician. Diarrhea can be the pharmacologic response to Zelnorm.

In two clinical studies of 4-8 weeks of duration designed to assess the safety and tolerability of Zelnorm in IBS patients with diarrhea as a predominant symptom (N=162), no serious adverse events were observed; 6% of Zelnorm-treated patients discontinued treatment due to diarrhea or abdominal pain.

### Abdominal Surgeries, Including Cholecystectomy

An increase in abdominal surgeries was observed on Zelnorm (9/2,965; 0.3%) vs. placebo (3/1,740; 0.2%) in the Phase 3 clinical studies. The increase was primarily due to a numerical imbalance in cholecystectomies reported in patients treated with Zelnorm (5/2,965; 0.17%) vs. placebo (1/1,740; 0.06%). A causal relationship between abdominal surgeries and Zelnorm has not been established.

The following list of adverse events includes those considered possibly related to Zelnorm, occurred in at least two patients in the Phase 3 clinical trials, and occurred more often on Zelnorm than placebo. Also included are those serious adverse events reported in the Zelnorm clinical program in at least two patients treated with Zelnorm, regardless of causality, or any serious adverse event considered possibly related to Zelnorm. Although the events reported occurred during treatment with Zelnorm, they were not necessarily caused by it.

**Body as a Whole:** pain, flushing, facial edema

**Cardiovascular:** hypotension, angina pectoris, syncope, arrhythmia, bundle branch block, supraventricular tachycardia

**Central Nervous System:** vertigo

**Female Reproductive:** ovarian cyst, miscarriage, menorrhagia

**Gastrointestinal:** irritable colon, fecal incontinence, tenesmus, increased appetite, eructation, increased SGOT, increased SGPT, bilirubinemia, cholecystitis, appendicitis, subileus

**Metabolic:** increased creatine phosphokinase

**Musculoskeletal:** back pain, cramps

**Neoplasms:** breast carcinoma

**Psychiatric:** attempted suicide, impaired concentration, emotional lability, increased appetite, sleep disorder, depression

**Respiratory:** asthma

**Skin:** pruritus, increased sweating

**Urinary:** albuminuria, frequent micturition, polyuria, renal pain

## Post Marketing Experience

Voluntary reports of adverse events occurring with the use of Zelnorm include the following: ischemic colitis (see PRECAUTIONS), mesenteric ischemia, gangrenous bowel, rectal bleeding, syncope, suspected sphincter of Oddi spasm, bile duct stone, and cholecystitis with elevated transaminases. Because these cases are reported voluntarily from a population of unknown size estimates of frequency cannot be made. No causal relationship between these events and Zelnorm use has been established. Hypokalemia secondary to diarrhea has also been reported.

## OVERDOSAGE

There have been no reports of human overdose with Zelnorm<sup>®</sup> (tegaserod maleate). Single oral doses of 120 mg of tegaserod were administered to 3 healthy volunteers in one study. All 3 subjects developed diarrhea and headache. Two of these subjects also reported intermittent abdominal pain, and 1 developed orthostatic hypotension. In 28 healthy subjects exposed to doses of tegaserod of 90 to 180 mg/d for several days, adverse events were diarrhea (100%), headache (57%), abdominal pain (18%), flatulence (18%), nausea (7%) and vomiting (7%).

Based on the large distribution volume and high protein binding of tegaserod it is unlikely that tegaserod could be removed by dialysis. In cases of overdose treat symptomatically and institute supportive measures as appropriate.

## DOSAGE AND ADMINISTRATION

The recommended dosage of Zelnorm<sup>®</sup> (tegaserod maleate) is 6 mg taken twice daily orally before meals for 4 to 6 weeks. For those patients who respond to therapy at 4-6 weeks, an additional 4-6 week course can be considered.

## HOW SUPPLIED

Zelnorm<sup>®</sup> (tegaserod maleate) is available as whitish to slightly yellowish, marbled, circular flat tablets with a bevelled edge containing 2 mg or 6 mg tegaserod as follows:

**2 mg Tablet** - white round engraved with "NVR" and "DL"

Unit Dose (blister pack)  
 Box of 60 (strips of 10).....NDC 0078-0355-80

**6 mg Tablet** - white round engraved with “NVR” and “EH”

Unit Dose (blister pack)  
 Box of 60 (strips of 10).....NDC 0078-0356-80

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

See USP Controlled Room Temperature. Protect from moisture.

T2002-18

## Information for the Patient

### Zelnorm<sup>®</sup> (tegaserod maleate)

#### Tablets

(pronounced ZEL-norm, te-gas-a-rod mal-ē-ate)

#### Rx only

Read this information carefully before you start taking Zelnorm<sup>®</sup> (ZEL-norm). Read the information you get each time you get more Zelnorm. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

#### What is the most important information I should know about Zelnorm?

If you get new or worse abdominal (stomach) pain, or blood in your stools, stop taking Zelnorm right away and tell your doctor. Your doctor may need to do tests to find out if you have a serious problem. Sometimes Zelnorm causes diarrhea. Stop taking Zelnorm and call your doctor right away if you get so much diarrhea that you get light-headed, dizzy, or faint.

#### What is Zelnorm?

Zelnorm is a medicine for the short-term treatment of women who have irritable bowel syndrome (IBS) with constipation (not enough or hard bowel movements) as their main bowel problem. Women with this medical condition suffer from abdominal pain or discomfort, bloating, and constipation. Zelnorm does not work for all women that use it. Zelnorm has not been shown to work in men with IBS.

Zelnorm increases the movement of stools (bowel movement) through the bowels. Zelnorm does not cure IBS. For those who are helped, Zelnorm reduces pain and discomfort in the abdominal area, bloating, and constipation. If you stop taking Zelnorm, your IBS symptoms may return within 1 or 2 weeks.

#### Who should not take Zelnorm?

You should not start taking Zelnorm if:

- You now have diarrhea or have diarrhea often.
- You have bad kidney or liver disease.
- You have ever had bowel obstruction (intestinal blockage), symptomatic gallbladder disease, or abdominal adhesions causing pain and/or intestinal blockage.
- You are allergic to Zelnorm or any of its ingredients. The active ingredient in Zelnorm is tegaserod maleate. The inactive ingredients are listed at the end of this leaflet.

### **Zelnorm may not be right for you. Tell your doctor if you:**

- Are pregnant or plan to become pregnant. Zelnorm is not recommended for use by pregnant women.
- Are breast-feeding. Do not breast-feed while you are taking Zelnorm. The drug is likely to pass into breast milk.
- Are taking or planning to take any other medicines, including those you can get without a prescription.

### **How should I take Zelnorm?**

- You should take Zelnorm twice a day on an empty stomach shortly before you eat a meal, or as your doctor prescribes it.
- You should take Zelnorm for 4 to 6 weeks to treat your IBS symptoms. If you feel better, your doctor may prescribe an additional 4 to 6 weeks of Zelnorm.
- If you miss a dose of Zelnorm, just skip that dose. Do not take two tablets to make up the missed dose. Instead, just wait until the next time you are supposed to take it and then take your normal dose.

### **What are the possible side effects of Zelnorm?**

Headache and diarrhea were the most common side effects seen with Zelnorm.

Diarrhea was an occasional side effect of treatment with Zelnorm. Most people who got diarrhea had it during the first week after starting Zelnorm. Typically, diarrhea went away with continued therapy. If you get bad diarrhea, or if you get diarrhea together with bad cramping, abdominal pain, fainting or dizziness, tell your doctor. Your doctor may tell you to stop taking Zelnorm or suggest other ways to manage your diarrhea.

In studies a very small number of patients were reported to have abdominal surgery. There were a few more reports of abdominal surgery in patients taking Zelnorm than in patients taking a sugar pill. Most of these were related to the gallbladder. It is not known if Zelnorm may increase your chance of abdominal surgery. Gallbladder surgery has been reported to occur more often in IBS patients than in the general population.

This list is not complete. Your doctor or pharmacist can give you a more complete list of possible side effects. Talk to your doctor about any side effects you may have.

### **General information about the safe and effective use of Zelnorm**

Keep Zelnorm at room temperature. Do not use Zelnorm past the expiration date shown on the package.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Zelnorm for a condition for which it was not prescribed. Do not give Zelnorm to other people, even if they have the same symptoms that you have. This leaflet summarizes the most important information about Zelnorm. For more information, talk with your doctor. You can ask your doctor or pharmacist for information about Zelnorm that is written for health professionals. You can also contact the company that makes Zelnorm at 1-866-427-6682 or [www.zelnorm.com](http://www.zelnorm.com).

**Inactive Ingredients:** Crospovidone, glyceryl monostearate, hypromellose, lactose monohydrate, poloxamer 188, and polyethylene glycol 4000.

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Novartis Pharma Stein AG  
Schaffhauserstrasse  
CH-4332 Stein, Switzerland

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Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936

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**IMPORTANT DRUG WARNING**

Dear Health Care Professional:

Novartis is writing to inform you of an important drug warning and important prescribing information which has been incorporated into the labeling for Zelnorm<sup>®</sup> (tegaserod maleate) tablets. Zelnorm is a serotonin 5-HT<sub>4</sub> receptor partial agonist indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. This new information relates to a Warning for serious consequences of diarrhea and a Precaution for rare reports of ischemic colitis in post-marketing use of Zelnorm.

**IMPORTANT DRUG WARNING**

Novartis has updated the package insert to include a Warning on diarrhea. This reflects rare cases where serious consequences of diarrhea (including hypovolemia, hypotension, and syncope) have been reported in clinical trials and during marketed use of Zelnorm.

**WARNINGS**

Serious consequences of diarrhea, including hypovolemia, hypotension, and syncope have been reported in the clinical studies and during marketed use of Zelnorm. In some cases, these complications have required hospitalization for rehydration. Zelnorm should be discontinued immediately in patients who develop hypotension or syncope. Zelnorm should not be initiated in patients who are currently experiencing or frequently experience diarrhea (see ADVERSE REACTIONS).

In addition, the section of the package insert titled “Zelnorm-Induced Diarrhea” in the Adverse Reactions section has also been revised to include a new sentence (see underlined text).

**ADVERSE REACTIONS****Zelnorm-Induced Diarrhea**

In the Phase 3 clinical studies, 8.8% of patients receiving Zelnorm reported diarrhea as an adverse experience compared to 3.8% of patients receiving placebo. The majority of the Zelnorm patients reporting diarrhea had a single episode. In most cases, diarrhea occurred within the first week of treatment. Typically, diarrhea resolved with continued therapy. Overall, the discontinuation rate from the studies due to diarrhea was 1.6% among the Zelnorm-treated patients. In clinical studies, a small number of patients (0.04%) experienced clinically significant diarrhea including hospitalization, hypovolemia, hypotension and need for intra-venous fluids. Patients who experience severe diarrhea during therapy with Zelnorm should be directed to consult their physician. Diarrhea can be the pharmacologic response to Zelnorm.

In two clinical studies of 4-8 weeks of duration designed to assess the safety and tolerability of Zelnorm in IBS patients with diarrhea as a predominant symptom (N=162), no serious adverse events were observed; 6% of Zelnorm-treated patients discontinued treatment due to diarrhea or abdominal pain.

Accordingly, the patient prescribing information, “Information for the Patient”, has also been revised to include the following information:

**What is the most important information I should know about Zelnorm?**

If you get new or worse abdominal pain with or without blood in your stools, stop taking Zelnorm right away and tell your doctor. Your doctor may need to do tests to find out if you have a serious problem.

Sometimes Zelnorm causes diarrhea. Stop taking Zelnorm and call your doctor right away if you get so much diarrhea that you get light-headed, dizzy, or faint.

### **IMPORTANT PRESCRIBING INFORMATION**

Rare post-marketing reports of ischemic colitis and other forms of intestinal ischemia have been reported during marketed use of Zelnorm. Placebo-controlled clinical trials of 7,000 patients for 3-month duration showed no cases of these events and would suggest the rate of these events is low. Novartis has updated the package insert to include a Precaution that includes information on these safety reports. A causal relationship between Zelnorm use and these events has not been established.

The Precautions section of the labeling has been revised as follows:

#### **PRECAUTIONS**

##### **Ischemic Colitis**

Ischemic colitis and other forms of intestinal ischemia have been reported in patients receiving Zelnorm during marketed use of the drug (see ADVERSE REACTIONS: Post-Marketing Experience). A causal relationship between Zelnorm use and these events has not been established. Placebo-controlled clinical trials of 7,000 patients for 3-month duration showed no cases of these events and would suggest the rate of these events is low. Zelnorm should be discontinued immediately in patients who develop symptoms of ischemic colitis, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain. Patients developing these symptoms should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with Zelnorm should not be resumed in patients who develop findings consistent with ischemic colitis.

Accordingly, a new sentence has also been added to the Precautions section titled “Information to Patients”.

##### **Information for Patients**

Patients should stop Zelnorm treatment and consult their physician if they experience new or worsening abdominal pain with or without rectal bleeding.

In addition, the section of the package insert titled “Post-Marketing Experience” in the Adverse Reactions section has been revised to include new information on safety reports received during marketed use of Zelnorm (see underlined text).

#### **ADVERSE REACTIONS**

##### **Post Marketing Experience**

Voluntary reports of adverse events occurring with the use of Zelnorm include the following: ischemic colitis (see PRECAUTIONS), mesenteric ischemia, gangrenous bowel, rectal bleeding, syncope, suspected sphincter of Oddi spasm, bile duct stone, and cholecystitis with elevated transaminases. Because these cases are reported voluntarily from a population of unknown size estimates of frequency cannot be made. No causal relationship between these events and Zelnorm use has been established. Hypokalemia secondary to diarrhea has also been reported.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of Zelnorm to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936 by phone (888) NOW-NOVARTIS or (888-669-6682) or the internet at <http://www.novartis.com>.

Alternatively, this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile 1-800-FDA-0178, by mail using the Form 3500 at <http://www.fda.gov/medwatch/index.html>.

Please see the enclosed revised package insert for complete prescribing information.

Sincerely,

Alan L. Bess, MD

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Clinical Safety and Epidemiology

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