Zelnorm Package Insert

NOVARTIS

T2004-53/T2004-54

89015305

Zelnorm®
(tegaserod maleate)

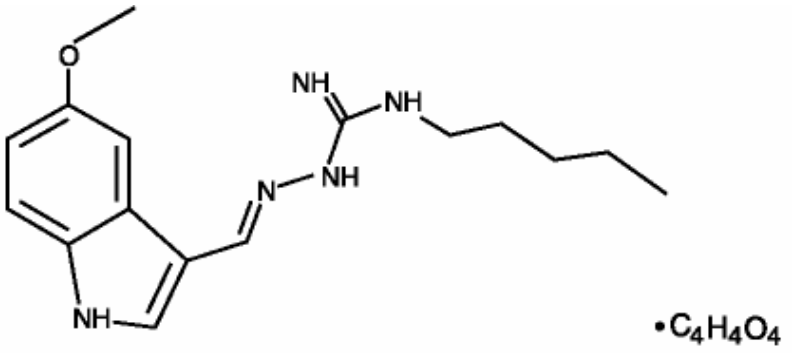
Tablets

Rx only

Prescribing Information

DESCRIPTION

Zelnorm® (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 $C_{16}H_{23}N_5O \bullet C_4H_4O_4$. 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 in the following tablet formulations:

- 2 mg and 6 mg tablets (blister packs) containing 2 mg and 6 mg tegaserod, respectively and the following inactive ingredients: crospovidone, glyceryl monostearate, hypromellose, lactose monohydrate, poloxamer 188, and polyethylene glycol 4000
- 6 mg tablets (bottles) containing 6 mg tegaserod and the following inactive ingredients: crospovidone, glyceryl behenate, hypromellose, lactose monohydrate, colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Irritable bowel syndrome with constipation and chronic idiopathic constipation are both lower gastrointestinal dysmotility disorders. 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), while in patients with chronic idiopathic constipation, reduced intestinal motility is the predominant cause of the condition. 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 both IBS and idiopathic constipation. 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_4) receptors in the maintenance of gastrointestinal functions in humans. 5-HT_4 receptor mRNA has been found throughout the human gastrointestinal tract.

Tegaserod is a 5-HT_4 receptor partial agonist that binds with high affinity at human 5-HT_4 receptors, whereas it has no appreciable affinity for 5-HT_3 or dopamine receptors. It has moderate affinity for 5-HT_1 receptors. Tegaserod, by acting as an agonist at neuronal 5-HT_4 receptors, triggers the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. The activation of 5-HT_4 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_{max} 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_{max} 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 5-HT_4 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 ($T_{1/2}$) 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. The pharmacokinetics of tegaserod in patients with chronic idiopathic constipation have not been studied.

Reduced Renal Function: No change in the pharmacokinetics of tegaserod was observed in subjects with severe renal impairment requiring hemodialysis (creatinine clearance $\leq$15 mL/min/1.73 m^2). C_{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_{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 who have IBS with constipation is not necessary.

CLINICAL STUDIES

IBS with Constipation

RESULTS IN WOMEN: 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® (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 ≥ 25% of the time over a 3-month period: < 3 bowel movements/week, hard or lumpy stools, or straining with a bowel movement. The 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.

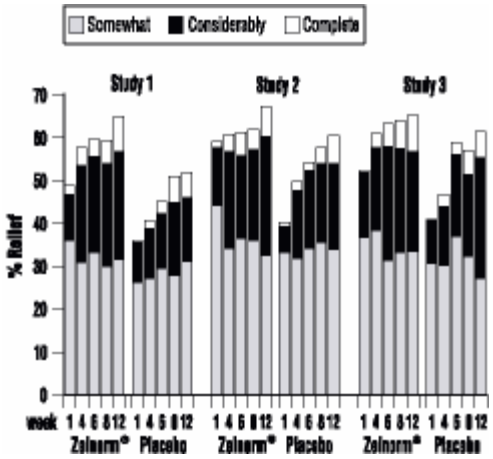
Each week of the 4-week placebo-free baseline period and the 12-week double-blind treatment period, patients were asked the question, "Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel 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.

	Month 1			**Month 3**		
	Proportion of Responders (Females)			**Proportion of Responders (Females)**		
Study	**Zelnorm® 6 mg b.i.d.**	**Placebo**	**Difference (95% Confidence Interval)**	**Zelnorm® 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: ≥ 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 female 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.

RESULTS IN MEN: In two randomized, placebo-controlled, double-blind studies enrolling 288 males, there were no significant differences between placebo and Zelnorm response rates in subgroup analyses by gender.

Chronic Idiopathic Constipation

In two multicenter, double-blind, placebo-controlled studies, 2,612 patients with chronic constipation were randomized to receive either Zelnorm® (tegaserod maleate) 6 mg b.i.d., 2 mg b.i.d., or placebo.

RESULTS IN PATIENTS UNDER AGE 65: A total of 2,281 patients were less than 65 years of age. Patients (91% female, mean age 43 [range 18-64], 90% Caucasian, 4.3% African American) had constipation defined as less than 3 complete spontaneous bowel movements [CSBM] per week and at least one of the following symptoms for at least 25% of defecations: straining, hard/very hard stools, incomplete evacuation. A bowel movement was evaluated by the patient as complete if it resulted in a feeling of complete emptying of their bowel. A bowel movement was considered to be spontaneous [SBM] if no laxatives were taken in the preceding 24 hours. The study population consisted of patients with a 6 month or longer history of constipation symptoms (median 12 years). Patients with constipation known to be due to other known colon diseases, pelvic floor dysfunction, metabolic or neurological disturbances, or concomitant medications were excluded.

After a 2-week baseline, patients were randomized to a 12-week double-blind treatment with Zelnorm 6 mg b.i.d., Zelnorm 2 mg b.i.d., or placebo. This treatment period was followed, in Study 1, by an extension period where patients received either 6 mg b.i.d. or 2 mg b.i.d. for an additional 13 months. The drop out rate for lack of efficacy for the additional 13-month period was 19% for 6 mg b.i.d. and 22% for 2 mg b.i.d.. In Study 2, the 12-week treatment period was followed by a 4-week drug-free withdrawal period.

Patients were classified as responders (primary efficacy variable) if they achieved an average increase of at least one CSBM per week during the first four weeks of treatment compared to baseline, and had at least 7 days of exposure in the study.

The response rate for the primary efficacy variable in patients under 65 years of age was higher in the Zelnorm 6 mg b.i.d. group compared to the placebo group for each of the 2 trials ($p < 0.0001$, Table 2). This difference was statistically significant for CSBM changes averaged over the first 4 weeks of treatment and the full 12 weeks of treatment. The results with Zelnorm 2 mg b.i.d. showed significant changes during the first 4 weeks, however, no statistically significant changes were observed over 12 weeks in one study.

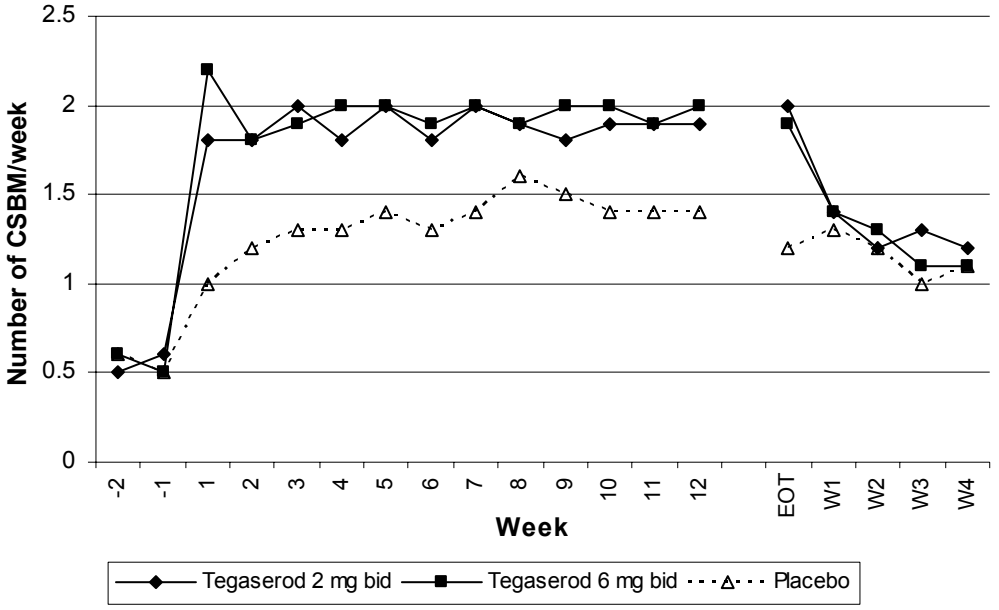
Proportion Of Patients Under Age 65 With An Increase Of 1 Or More CSBM For The Two Trials Combined

	Zelnorm® 6 mg b.i.d.	Zelnorm® 2 mg b.i.d.	Placebo
Weeks 1-4	43% (337/789)	39% (286/732)	25% (184/737)
Weeks 1-12	45% (355/789)	38% (281/732)	28% (206/737)

Infrequent defecation

At baseline, the median number of CSBM's per week was zero and the mean number of CSBM's per week was 0.5. Regardless of baseline, Zelnorm significantly increased the number of complete spontaneous bowel movements compared to placebo at each week. ($p<0.05$).

Frequency Of Complete Spontaneous Bowel Movement (CSBM) Over 12 Week Treatment And 4 Week Withdrawal Period In Study 2



Zelnorm also significantly increased the number of SBM's compared to placebo at each week ($p<0.05$).

Constipation symptoms

Patients treated with Zelnorm experienced a statistically significant reduction in the individual symptoms of straining, abdominal distention/bloating, and abdominal discomfort/pain, and a statistically significant improvement in stool consistency and frequency compared to placebo when averaged over the 12 weeks ($p<0.05$). In addition, a global constipation relief score, computed as an average of 4 scores measuring abdominal discomfort/pain, abdominal distention/bloating, bothersomeness of constipation and satisfaction with bowel habits, showed statistically significant improvement for Zelnorm compared to placebo when averaged over the 12 weeks ($p<0.05$).

RESULTS IN PATIENTS AGE 65 AND OVER: Subgroup analyses of patients 65 and older (n=331) showed no significant treatment effects for Zelnorm over placebo.

INDICATIONS AND USAGE

IBS with Constipation

Zelnorm® (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 with IBS with constipation have not been established.

Chronic Idiopathic Constipation

Zelnorm® (tegaserod maleate) is indicated for the treatment of patients less than 65 years of age with chronic idiopathic constipation. The effectiveness of Zelnorm in patients 65 years or older with chronic idiopathic constipation has not been established (see Geriatric Use).

The efficacy of Zelnorm for the treatment of IBS with constipation or chronic idiopathic constipation has not been studied beyond 12 weeks.

CONTRAINDICATIONS

Zelnorm® (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 severe diarrhea, hypotension or syncope. Zelnorm should not be initiated in patients who are currently experiencing or frequently experience diarrhea (see ADVERSE REACTIONS).

PRECAUTIONS

General

Zelnorm® (tegaserod maleate) 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). In some cases, hospitalization was required. 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 experiencing 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 or other forms of intestinal ischemia.

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. Diarrhea can be a pharmacologic response to Zelnorm. 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 $AUC_{0\text{-}24\ hr}$) 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 $AUC_{0\text{-}24\ hr}$). 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 $AUC_{0\text{-}24\ hr}$) or 60 mg/kg/day (approximately 3 to 4 times the human exposure at 6 mg b.i.d. based on plasma $AUC_{0\text{-}24\ hr}$).

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 $AUC_{0\text{-}24\ hr}$) in male rats and 150 mg/kg/day (approximately 42 times the human exposure at 6 mg b.i.d. based on plasma $AUC_{0\text{-}24\ hr}$) 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 $AUC_{0\text{-}24\ hr}$) 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 $AUC_{0\text{-}24\ hr}$) 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

Zelnorm has not been studied in pediatric patients.

Geriatric Use

IBS with Constipation

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 were observed between these patients and younger patients with regard to adverse events.

No dose adjustment is necessary when administering Zelnorm to patients with IBS with constipation over 65 years old. (See CLINICAL PHARMACOLOGY.)

Chronic Idiopathic Constipation

Of 2,612 patients in Phase 3 clinical studies of Zelnorm, 331 were at least 65 years of age. Efficacy in patients 65 years of age or greater showed no significant difference between drug and placebo responses. Patients 65 years of age or greater who received Zelnorm experienced a higher incidence of diarrhea and discontinuations due to diarrhea than patients younger than 65.

ADVERSE REACTIONS

IBS with Constipation

In Phase 3 clinical trials 2,632 female and male patients received Zelnorm® (tegaserod maleate) 6 mg b.i.d. or placebo. The frequency and type of adverse events for females and males were similar. 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® (tegaserod maleate) than Placebo

System/ Adverse Experience	**Zelnorm® 6 mg b.i.d. (n=1,327)**	**Placebo (n=1,305)**
Gastrointestinal System Disorders		
Abdominal Pain	12%	11%
Diarrhea	9%	4%
Nausea	8%	7%
Flatulence	6%	5%
Central and Peripheral Nervous System		
Headache	15%	12%
Dizziness	4%	3%
Migraine	2%	1%
Body as a Whole - General Disorders		
Accidental Trauma	3%	2%
Leg Pain	1%	< 1%
Musculoskeletal System Disorders		
Back Pain	5%	4%

Arthropathy	2%	1%

Chronic Idiopathic Constipation

In phase 3 clinical trials 2,603 male and female patients received Zelnorm 6 mg b.i.d., 2 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 than in patients who received placebo.

Adverse Events Occurring in ≥ 1% of Chronic Idiopathic Constipation Patients And More Frequently On Either Dose of Zelnorm® Than Placebo

System/ Adverse Experience	**Zelnorm® 6 mg b.i.d. (n=881)**	**Zelnorm® 2 mg b.i.d. (n=861)**	**Placebo (n=861)**
Gastrointestinal System Disorders			
Diarrhea	7%	4%	3%
Abdominal pain	5%	6%	5%
Nausea	5%	5%	4%
Abdominal distension	4%	3%	4%
Abdominal pain upper	2%	2%	2%
Vomiting	2%	1%	1%
Central and Peripheral Nervous System			
Dizziness	2%	1%	2%
Insomnia	2%	1%	1%
Headache aggravated	1%	1%	0%
General disorders and administration site conditions			
Fatigue	1%	1%	1%
Infections and infestations			
Upper respiratory tract infection	4%	3%	2%
Sinusitis	3%	3%	2%
Fungal infection	0%	1%	1%
Musculoskeletal and connective tissue disorders			
Back Pain	3%	2%	3%
Myalgia	1%	1%	1%
Reproductive system and breast disorders			
Dysmenorrhoea	1%	2%	1%
Respiratory, thoracic and mediastinal disorders			
Pharyngitis	1%	1%	1%
Sinus congestion	1%	0%	1%
Renal and urinary disorders			
Urinary tract infection	1%	2%	1%
Skin and subcutaneous tissue disorders			
Rash	1%	1%	0%
Pruritus	0%	1%	0%

Zelnorm was not associated with changes in ECG intervals.

Zelnorm-Induced Diarrhea

IBS with Constipation

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 intravenous fluids. Diarrhea can be the pharmacologic response to Zelnorm.

Chronic Idiopathic Constipation

In the two Phase 3 studies, 6.6% of patients treated with Zelnorm 6 mg b.i.d. and 4.2% of patients treated with Zelnorm 2 mg b.i.d. reported diarrhea as an adverse event, versus 3.0% of patients receiving placebo.

The diarrhea episodes experienced by patients treated with tegaserod occurred early after initiation of treatment (median of 5.5 days), were of short duration (median of 2.5 days), and occurred only once in the majority of patients.

Typically, diarrhea resolved with continued therapy; only 0.9% of patients treated with Zelnorm 6 mg b.i.d. discontinued the study due to diarrhea (compared to 0.3% in the Zelnorm 2 mg b.i.d. group and 0.2% in the placebo group).

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 IBS 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%). In chronic idiopathic constipation clinical trials there was no increase in the frequency of abdominal and pelvic surgeries in active versus placebo groups: 9/1752; 0.5% on Zelnorm versus 8/861; 0.9% on placebo. A causal relationship between abdominal surgeries and Zelnorm has not been established.

Other adverse events

The following list of adverse events includes those from phase 3 clinical studies (6 mg b.i.d. or 2 mg b.i.d.) which were reported more frequently (>0.2%) in patients on Zelnorm than placebo; or which were considered by the investigator to be possibly related to Zelnorm and reported more frequently (>0.1%) on Zelnorm than placebo; or which lead to discontinuation more frequently (≥0.1% and in more than 1 patient) on Zelnorm than placebo. The list also contains those serious adverse events from all clinical trials in patients treated with either 6 mg b.i.d. or 2 mg b.i.d. Zelnorm which were either considered by the investigator as possibly drug related, or occurred in at least 2 more patients on Zelnorm than on placebo. Although the events reported occurred during treatment with Zelnorm, they were not necessarily caused by it.

Cardiac disorders: Angina pectoris, supraventricular tachycardia, syncope

Ear and labyrinth disorders: Vertigo

Eye disorders: Visual disturbance

Gastrointestinal disorders: Hemorrhoids, proctalgia, stomach discomfort, fecal incontinence, irritable bowel syndrome, dyspepsia, gastroesophageal reflux, gastritis

General disorders and administration site conditions: Chest pain, peripheral edema

Hepatobiliary disorders: Cholelithiasis

***Immune system disorders*:** Hypersensitivity reactions

Investigations: Creatinine phosphokinase increased, increased eosinophil count, low neutrophil count

Metabolism and nutrition disorders: increased appetite

***Neoplasms benign, malignant and unspecified (including cysts and polyps)**:* Breast carcinoma

Psychiatric disorders: Depression, sleep disorder, restlessness

Respiratory, thoracic and mediastinal disorders: Dyspnea, pharyngolaryngeal pain

Reproductive system and breast disorders: Miscarriage, menorrhagia

Surgical and medical procedures: Cholecystectomy

Vascular disorders: Flushing, hypotension

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, hypotension, hypovolemia, electrolyte disorders, suspected sphincter of Oddi spasm, bile duct stone, cholecystitis with elevated transaminases, and hypersensitivity reaction including rash, urticaria, pruritus and serious allergic Type I reactions. 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.

Post-marketing reports of diarrhea, which can be a pharmacologic response to Zelnorm, have also been received.

OVERDOSAGE

There have been no reports of human overdosage with Zelnorm® (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 overdosage treat symptomatically and institute supportive measures as appropriate.

DOSAGE AND ADMINISTRATION

IBS with Constipation: The recommended dosage of Zelnorm® (tegaserod maleate) is 6 mg taken twice daily orally before meals for 4 to 6 weeks. For those women who respond to therapy at 4-6 weeks, an additional 4-6 week course can be considered.

Chronic Idiopathic Constipation: The recommended dosage of Zelnorm is 6 mg taken twice daily orally before meals. Physicians and patients should periodically assess the need for continued therapy.

HOW SUPPLIED

Zelnorm® (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 or bottle)

Box of 60 (strips of 10)….....NDC 0078-0356-80
Bottle of 60 .....NDC 0078-0426-20
Bottle of 500 .....NDC 0078-0426-08

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

See USP Controlled Room Temperature. Protect from moisture.

T2004-53

Information For The Patient

PPI 2004-08

Zelnorm®
(tegaserod maleate)

Tablets

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

Rx only

Read this information carefully before you start taking Zelnorm® (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 with your bowel that may require special treatment or hospitalization.

Sometimes Zelnorm causes diarrhea. Stop taking Zelnorm and call your doctor right away if you get so much diarrhea that you get lightheaded, 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. Zelnorm does not work for all women who use it. Zelnorm has not been shown to work in men with IBS with constipation.
- the treatment of patients less than 65 years of age with chronic idiopathic constipation. Chronic constipation means constipation lasting over 6 months. Idiopathic constipation means constipation not due to other diseases or drugs. Zelnorm has not been shown to work in patients with chronic idiopathic constipation who are 65 years of age or older.

Zelnorm increases the movement of stools (bowel movement) through the bowels. Zelnorm does not cure IBS with constipation or chronic idiopathic constipation. For those with IBS with constipation who are helped, Zelnorm reduces pain and discomfort in the abdominal area, bloating, and constipation. For those with chronic idiopathic constipation, Zelnorm increases bowel movements, reduces straining, bloating and abdominal discomfort If you stop taking Zelnorm, your 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.
- For IBS with Constipation: 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.
- For Chronic Idiopathic Constipation: You should talk to your doctor regularly about whether you need to stay on 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.

There have been rare cases of rectal bleeding and severe abdominal pain in patients treated with Zelnorm. Some of these problems were related to insufficient blood flow to part of the bowel. It is not known if this was related to Zelnorm use.

In studies a very small number of patients were reported to have abdominal surgery. In IBS with constipation studies 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.

Inactive Ingredients: Zelnorm is available for oral use in the following tablet formulations:

- 2 mg and 6 mg tablets (blister packs) containing the following inactive ingredients: crospovidone, glyceryl monostearate, hypromellose, lactose monohydrate, poloxamer 188, and polyethylene glycol 4000
- 6 mg tablets (bottles) containing the following inactive ingredients: crospovidone, glyceryl behenate, hypromellose, lactose monohydrate, colloidal silicon dioxide.

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NOVARTIS

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