

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו.

ZELMAC[®] (tegaserod)

Prescribing Information

1. Name of the medicinal product

ZELMAC[®] 6 mg tablets.

2. Qualitative and quantitative composition

One tablet contains 6 mg tegaserod (as hydrogen maleate). For excipients, see section 6.1. List of excipients.

3. Pharmaceutical form

Tablets

Circular, flat, with bevelled edges, whitish to slightly yellowish, marbled, marked 'EH' on one side and 'NVR' on the other.

4. Clinical particulars

4.1. Therapeutic indications

Irritable Bowel syndrome (IBS)

Treatment of abdominal pain and discomfort, bloating, and altered bowel function in women with irritable bowel syndrome (IBS) whose main symptoms are pain/discomfort and constipation for a maximum of 12 weeks.

The safety and effectiveness of Zelmec in men with IBS with constipation have not been established.

Chronic Idiopathic Constipation

Treatment of patients less than 65 years of age with chronic idiopathic constipation. The effectiveness of Zelmac in patients 65 years or older with chronic idiopathic constipation has not been established.

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

4.2. Posology and method of administration

Irritable Bowel Syndrome (IBS) and chronic Idiopathic constipation

The recommended dose of Zelmac is one 6 mg tablet twice daily. Zelmac is to be taken orally prior to a meal for up to 12 weeks.

Elderly patients

No dosage adjustment is required in elderly patients.

Paediatric patients

Safety and efficacy have not been established in paediatric patients. Use in this patient population is therefore not recommended.

Patients with hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment. However, caution is recommended when using tegaserod in this patient population.

Although mild to moderate impairment did not significantly alter the pharmacokinetics of tegaserod, a worsening of hepatic function (of which decreased serum albumin and increased dihydroxy/trihydroxy bile acids are indicators) might result in elevated exposure to tegaserod (see section 5.2. Pharmacokinetic properties).

Zelmac has not been adequately studied in patients with moderate or severe hepatic impairment. , therefore it is not recommended in these patients (see section 5.2. Pharmacokinetic properties).

Patients with renal impairment

No dosage adjustment is required in patients with mild to moderate renal impairment. Tegaserod is not recommended in patient with severe renal impairment (see section 5.2. Pharmacokinetic properties).

4.3. Contraindications

- Hypersensitivity to tegaserod or to any of the excipients.
- Severe renal impairment
- Moderate or severe hepatic impairment
- A history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions

4.4. Special warnings and special precautions for use

Zelmac should not be initiated in patients who are currently experiencing or frequently experience diarrhea.

Patients who experience severe diarrhea during therapy with Zelmac (see section 4.8. Undesirable effects) should be directed to stop taking the medicine and to consult their physician.

Zelmac should be discontinued immediately in patients who develop hypotension or syncope (see section 4.8. Undesirable effects).

Zelmac contains lactose. Therefore patients with rare hereditary problems of galactose intolerance, severe lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Ischemic colitis, and other forms of intestinal ischemia, have been reported in patients receiving Zelmac during marketed use of the drug. A causal relationship between Zelmac use and these events has not been established. Zelmac 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.

4.5. Interaction with other medicinal products and other forms of interaction

No clinically relevant drug interactions were identified in specific drug-drug interaction studies or following concomitant use during the tegaserod clinical development programme.

Based on the currently available data, dosage adjustment is not required for either drug when Zelmac is coadministered with other drugs.

4.6. Pregnancy and lactation

Pregnancy

Data on a limited number (n=15) of exposed pregnancies indicate no adverse effects of tegaserod on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). However, in view of limited experience in humans, use of Zelmac during pregnancy is not recommended.

Lactation

Tegaserod is excreted in the milk of lactating rats with a high milk-to-plasma ratio. Since it may also be excreted in human milk, Zelmac should not be prescribed to women who are breast-feeding.

4.7. Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8. Undesirable effects

Irritable Bowel Syndrome

In placebo-controlled studies of 2198 patients treated with tegaserod for up to 12 weeks, the frequency of adverse events in patients receiving tegaserod was similar to that observed with placebo, with the exception of diarrhoea.

Diarrhoea was reported as an adverse event by 11.7% of patients under tegaserod treatment in clinical studies, whereas the corresponding figure for placebo was 5.4%. even in the subset of patients with more than 3 bowel movements/day or loose/watery stools up to 25% of the time at baseline, the frequency with which diarrhoea was reported as an adverse event during treatment was only slightly higher. In most cases it occurred early after initiation of treatment (median of 9 days), was transient (median duration 2 days), most often observed as a single episode during the 12-week treatment period and resolved with continued therapy. The rate of discontinuation from the studies due to diarrhoea was low (1.6% in tegaserod-treated patients and 0.5% in the placebo group).

In clinical studies, a small number of patients (0.04%) experienced clinically significant diarrhoea including hospitalization, hypovolemia, hypotension and need for intra-venous fluids. Diarrhoea can be the pharmacologic response to Zelmac.

The frequency of most other adverse events occurring in clinical studies was similar in tegaserod- and placebo-treated patients. They included gastrointestinal complaints (e.g. abdominal pain, nausea, and flatulence), headache, dizziness, back pain and influenza-like symptoms.

Chronic Idiopathic Constipation

In the two clinical trials in which 1742 patients with chronic constipation received tegaserod 6 mg b.i.d. or placebo for up to 12 weeks, the frequency of adverse events in patients receiving tegaserod was similar to that observed with placebo, with the exception of diarrhoea.

In the two Phase III studies, 6.6% of patients treated with tegaserod 6 mg b.i.d. reported diarrhoea, versus 3.0% of patients receiving placebo.

The diarrhoea 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, diarrhoea resolved with continued therapy; only 0.9% of patients treated with tegaserod 6 mg b.i.d. discontinued the study due to diarrhoea (compared to 0.2% in the placebo group). Patients who experience severe diarrhoea during therapy with tegaserod should be directed to consult their physician. Diarrhoea can be the pharmacologic response to tegaserod.

In irritable bowel syndrome with constipation (IBS-C) and chronic constipation clinical trials, tegaserod was not associated with changes in ECG intervals.

Post Marketing Experience

Spontaneous reports of adverse effects occurring with the use of Zelmac include very rare cases of hypokalaemia secondary to diarrhoea, very rare cases of ischaemic colitis and the following hypersensitivity reactions: rare cases of rash, urticaria and pruritus, and very rare cases of serious allergic type-1 reactions.

No causal relationship between the reported cases of ischaemic colitis events and Zelmac use has been established.

4.9. Overdose

Signs and symptoms

There is no experience of acute intoxication with tegaserod. However, on the basis of data from healthy volunteers given single oral doses equivalent to 116 mg tegaserod, the signs and symptoms of overdosage may include diarrhoea, headache, intermittent abdominal pain and orthostatic hypotension.

Treatment

Tegaserod is unlikely to be removed by means of dialysis because of its large distribution volume and its extensive binding to plasma proteins. In the event of overdose, symptomatic and supportive therapy should be given as appropriate.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 5-HT₄ (serotonin type-4) receptor partial agonist (ATC code: A03A E02).

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 constipation, dysfunction of intestinal motility and water secretion appears to be the predominant cause of the condition. The mechanism of action of tegaserod is shown in its stimulation of the peristaltic reflex and intestinal secretion and its inhibition of visceral sensitivity via activation of serotonin type-4 (5-HT₄) receptors in the gastrointestinal tract. Tegaserod binds with high affinity at human 5-HT₄ receptors, whereas it has no appreciable affinity for 5-HT₃ or dopamine receptors. Tegaserod acts as a partial agonist at neuronal 5-HT₄ receptors, triggering the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. 5-HT₄ receptor mRNAs have been found throughout the human gastrointestinal tract. *In vivo* studies showed tegaserod to enhance basal motor activity and normalise impaired motility throughout the gastrointestinal tract. In addition, studies demonstrated that it moderates visceral sensitivity during colorectal distension in animals. In an animal model of constipation, tegaserod normalized stool frequency and quantity, and softened stool consistency.

In clinical pharmacology studies, tegaserod displayed promotile activity throughout the gastrointestinal tract. In healthy subjects, tegaserod administered either as an intravenous infusion of 0.6 mg or as an oral dose of 6 mg significantly decreased gastric lag time, accelerated gastric emptying, and reduced small bowel and colonic transit time compared with placebo. Tegaserod displayed a strong trend in reducing the number of postprandial reflux episodes and acid exposure in patients with gastroesophageal reflux disease. In patients with IBS, tegaserod reduced small bowel transit time and facilitated colonic transit. Tegaserod consistently improved stool consistency and increased the number of bowel movements; these effects were most evident on the first day of treatment, and persisted throughout a 12-week treatment period in IBS patients. Clinical pharmacology data suggest an involvement of local mechanisms in the pharmacodynamic activities of tegaserod, in agreement with preclinical findings.

Irritable Bowel Syndrome

Clinical studies have shown that Zelmac provides relief of abdominal pain and discomfort, bloating and altered bowel function in IBS patients who identify abdominal pain/discomfort and constipation as their main symptoms. In two multicentre, double-blind, placebo-controlled studies, 1680 patients with at least a 3-month history of IBS symptoms including abdominal pain and altered bowel function were studied. In all patients, altered bowel function was characterised by two of three constipation symptoms at least 25 % of the time, specifically < 3 bowel movements/week, hard or lumpy stools, or straining with a bowel movement. In addition to these symptoms, 36 % of patients had at least one of the following symptoms at least 25 % of the time: > 3 bowel movements/day, loose or watery stools, or urgency. A 4-week placebo-free baseline period was followed by a 12-week treatment period. Patients rated their weekly response using the Subject's Global Assessment (SGA) of Relief, which took into account overall well-being, symptoms of abdominal pain and discomfort, and altered bowel function. Treatment with Zelmac was associated with a significant improvement in the SGA of Relief. This is supported by several other efficacy measurements relevant to IBS, namely reduction in abdominal pain/discomfort, reduction in number of days with significant bloating, increase in number of bowel movements, improvement in stool consistency, and reduction in number of days with no bowel movements.

The onset of action, as measured by the SGA of Relief, was observed as early as one week after the start of treatment and was sustained over the course of the 12-week treatment period. The patient's severity of symptoms, use of tricyclic antidepressants or selective serotonin reuptake inhibitors, or daily intake of dietary fibre did not appear to affect the efficacy of tegaserod.

Tegaserod did not have an effect on the QTc interval compared to placebo. This was consistent with preclinical findings.

In a 12-month open-label study, 579 patients were treated with tegaserod, 53% of whom completed the study. Of those patients who were responders at month three, 59 % were still responders after 12 months of treatment. The safety and tolerability profile was similar to that observed during the placebo-controlled phase 3 studies.

Chronic Constipation

The efficacy, safety and tolerability of tegaserod was studied in 2,603 patients with chronic constipation in two multi-centre, double-blind, placebo-controlled studies. Selected patients (88.2% female, mean age 47, 91% Caucasian, 3.9% African American) had constipation defined as less than 3 complete spontaneous bowel movements [CSBM]/week and at least one symptom from: straining, incomplete evacuation, hard/very hard stools. A bowel movement was evaluated as complete by the patient if it resulted in a feeling of complete emptying of their bowel and was considered a spontaneous bowel movement [SBM] if no laxatives were taken in the preceding 24 hours. To be included in the study, constipation was not to be caused by primary colon disease, pelvic floor dysfunction, metabolic or neurological disturbances, or concomitant medications.

After a 2-week baseline, patients were randomized to 12 weeks double-blind treatment with tegaserod 2 mg b.i.d., tegaserod 6 mg b.i.d., or placebo. This treatment period was followed, in Study 1, by an open label treatment period where patients received either 2 or 6 mg b.i.d. for an additional 13 months. In Study 2, the 12 weeks treatment period was followed by a 4-week drug free withdrawal period.

Patients were classified as responders (primary efficacy variable) if they achieved an 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 treatment.

The data from trials showed the following:

The response rate for the pre-defined primary efficacy variable was higher in the tegaserod 6 mg b.i.d. groups compared to the placebo group for each of the 2 trials and this difference was statistically significant (see Table 1).

Table 1: Response rate in clinical trials

Study	Weeks 1 to 4 Proportion of Responders			Weeks 1 to 12 Proportion of Responders		
	Tegaserod 6 mg b.i.d.	Placebo	P value	Tegaserod 6 mg b.i.d.	Placebo	P value
1	172/428 (40.2%)	110/412 (26.7%)	<0.0001	185/428 (43.3%)	126/412 (30.6%)	<0.0001
2	194/449 (43.2%)	111/442 (25.1%)	<0.0001	201/449 (44.8%)	119/442 (26.9%)	<0.0001

Response: increase of = 1 complete spontaneous bowel movements/week compared to baseline, and = 7 days of treatment.

5.2. Pharmacokinetic properties

Tegaserod is rapidly absorbed following oral administration; peak plasma concentrations are reached after approximately 1 hour. Absolute bioavailability is about 10 % under fasted conditions. Food reduced the bioavailability of tegaserod by 40-65 % and C_{max} by approximately 20-40%.

Tegaserod is approximately 98 % bound to plasma proteins, primarily to α_1 -acid glycoprotein. It is extensively distributed into tissues following intravenous administration, with a volume of distribution at steady state of 368 ± 223 l.

Tegaserod has two main metabolic pathways. The first involves presystemic acid-catalysed hydrolysis in the stomach, followed by oxidation and conjugation resulting in the main metabolite of tegaserod, 5-methoxy-indole-3-carboxylic acid glucuronide. The main metabolite has negligible affinity for 5-HT₄ receptors. In man, there was no statistically significant change in systemic exposure to tegaserod at neutral gastric pH values. The second metabolic pathway is direct glucuronidation which leads to generation of three isomeric N-glucuronides.

In vitro, 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 and was therefore studied *in vivo*. The main human metabolite did not inhibit the activity of any of the above cytochrome P450 isoenzymes.

The plasma clearance of tegaserod is 77 ± 15 l/h, with an estimated terminal half-life ($t_{1/2}$) of 11 ± 5 h following intravenous administration. Approximately two-thirds of an orally administered dose is excreted unchanged in the faeces, with the remaining one-third excreted in the urine, primarily as the main metabolite.

The pharmacokinetics of tegaserod are dose proportional over the range 2 to 12 mg given twice daily for five days, with no relevant accumulation of tegaserod in plasma.

The pharmacokinetics of tegaserod in IBS patients are comparable to those in healthy subjects and similar between males and females.

Special Populations

Elderly

The pharmacokinetics of tegaserod were similar between elderly and young males, whereas the mean AUC and C_{max} were 40 % and 22 % greater in elderly than in young females but still within the variability seen in healthy subjects.

Hepatic impairment

In subjects with mild to moderate hepatic impairment (liver cirrhosis), mean AUC was 43 % higher and C_{max} 18 % higher. No dosage adjustment is required in patients with mild impairment, however, caution is recommended when using tegaserod in this patient population. Although mild to moderate impairment did not significantly alter the pharmacokinetic of tegaserod, a worsening of hepatic function (of which decreased serum albumin and increased dihydroxy/trihydroxy bile acids are indicators) might result in elevated exposure to tegaserod.

Tegaserod has not been studied adequately in subjects with moderate or severe hepatic impairment and is therefore not recommended in these patients.

Renal impairment

No change in the pharmacokinetics of tegaserod was observed in subjects with severe renal impairment requiring haemodialysis (creatinine clearance ≤ 15 ml/min/1.73 m²).

No dosage adjustment is required in patients with mild to moderate renal impairment. Tegaserod is not recommended in patients with severe renal impairment because of the increase in AUC of the main metabolite M29 by 10-fold.

5.3. Preclinical safety data

A variety of preclinical safety studies with several animal species revealed no evidence of systemic or target organ toxicity. Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little significance to clinical use.

6. Pharmaceutical particulars

6.1. List of excipients

Crospovidone, Glyceryl monostearate, Hypromellose, Lactose monohydrate, Poloxamer 188, Macrogol 4000

6.2. Special precautions for storage

Store in the original package. Do not store above 30°C.

Zelmac must be kept out of the reach and sight of children.

6.3. Nature and contents of container

PVC/PE/PVDC or PA/AL/PVC blisters.

6.4. Instructions for use and handling

No special requirements

Manufacturer:

Novartis Pharmaceutica S.A., Spain

for: Novartis Pharma AG, Basel, Switzerland.

License Holder:

Promedico Ltd.

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