NOVARTIS

# Zelmacâ

Treatment of Irritable Bowel Syndrome (IBS)

COMPOSITION
One tablet contains 6 mg tegaserod (as hydrogen maleate)

PHARMACEUTICAL FORM
Zelmac tablets are circular, flat, with bevelled edges, whitish to slightly yellowish, marbled, marked “EH” on one side and “NVR” on the other. Each tablet contains 6 mg tegaserod (as tegaserod maleate). Zelmac is available in blister packs containing 10 or 30 tablet.

INDICATION
The treatment of irritable bowel syndrome (IBS), constipation predominant, particularly in female patients whose main symptoms are constipation and abdominal pain and/or discomfort.

Diagnosis of IBS should refer to Manning or Rome I or Rome II criteria. (see table 1, 2 and 3 in DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION
The recommended dose of ZELMAC is one 6 mg tablet twice daily. ZELMAC is to be taken orally prior to a meal. The maximum duration of treatment should be not longer than 12 weeks and treatment should be discontinued if there has been no response after 4 weeks.

Diagnosis of IBS should refer to Manning or Rome I or Rome II criteria. (see table 1,2 and 3)

Table 1. the Manning criteria for diagnosis of IBS.

Four symptoms were significantly more common among patients with IBS:
- Looser stools at onset of pain
- More frequent bowel movement at onset of pain
- Pain eased after bowel movement
- Visible (abdominal ) distension

Two further symptoms were more common among patients with IBS
- Passage of mucus
- Feeling of incomplete evacuation

Table 2. Rome I criteria for diagnosis of IBS.

At least 3 months continuous or recurrent symptoms of:

1. Abdominal pain or discomfort which is:
   - Relieved with defecation
   - And/ or associated with a change in frequency of stool
   - And / or associated with a change in consistency of stool

   And
2. Two or more of the following, at least a quarter of occasion or days:
   - Altered stool frequency
   - Altered stool form (lumpy/ hard or loose/ watery)
   - Altered stool passage ((straining or urgency, feeling of incomplete evacuation)
   - Passage of mucus
   - Bloating or feeling of abdominal distension.

Table 3. Rome II criteria for diagnosis of IBS.

At least 12 weeks, which need not be consecutive in the precceding 12 months of abdominal discomfort or pain that has two of three features :

- Relieved with defecation and /or
- Onset associated with a change frequency of stool and/ or
- Onset associated with a change in form (appearance of stool).

The following symptoms cumulatively support the diagnosis of IBS

- Abnormal stool frequency
- Abnormal stool form (lumpy/hard or loose/watery stool)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients in the formulation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with hepatic impairment

No dosage adjustment is required in patients with severe hepatic impairment. And therefore is not recommended for patients in this group.

Patients with renal impairment

Zelmac is not recommended for patients with severe renal impairment.

Use in children.

The safety and efficacy have not been established in pediatric patients. Therefore, Zelmac is not recommended in this population.

Effects on ability to drive and use machines.

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

Carcinogenicity and Mutagenicity

Long-term studies in mice showed increased incidences of mucosal hyperplasia and adenocarcinoma of the small intestine. The tumours occurred at a dietary dose (600 mg/kg/day) corresponding to exposures 17x the expected human exposure, based on AUC.

The no effect level of hyperplasia and tumours resulted in exposure 17 x and 34 x the expected human respectively. There were no drug-related increase in tumour incidences in a rat carcinogenicity study at up to 180 mg/kg/day in the diet, with exposures 172 x the expected human exposure, based on AUC.

There was no evidence of genotoxicity in test for chromosomal aberrations (Chinese hamsterV79 cells in vitro and mouse micronucleous assay in vivo) and DNA damage (unscheduled DNA synthesis in vitro). Tegaserod produced a weak positive result in one strain of Salmonella typhimurium in a bacteria mutation assay , but this finding could not be reproduced in four follow up tests, and an in vitro gene mutation assay in Chinese hamster V79 cells was negative.

Impairment of fertility
Effects on fertility were studies in rats. Dietary administration of tegaserod had no adverse effects on reproductive performance of males at up to 240 mg/kg/day equivalent to exposures 64 time the human exposure based on AUC. Corpora lutea, implantation sites and litter sizes were decreased and maternal toxicity observed at doses of 300 mg/kg/day (93 times the human exposure at the maximum recommended dose, based on AUC).

Use in pregnancy (Category B3)
In animal studies, tegaserod and/or its metabolites crossed the placenta of rats and rabbits. There is no evidence of teratogenic effects due to tegaserod in studies with rats and rabbits at oral doses up to 100 mg/kg/day and 120 mg/kg/day, respectively (12 and 40 times human exposure at the maximum human clinical dose based on AUC, respectively ) and, by dietary doses of 300 mg/kg/day in rats (93 times the expected human exposure). Fetal effects observed in rats dosed with tegaserod by gavage included increased perinatal loss and reduced fetal weights at 150 mg/kg/day in the diet (55 times the human exposure, based on AUC). There are, however, no adequate well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, tegaserod should be used during pregnancy only if clearly needed.

Lactation
Tegaserod is excreted in the milk of lactating rats with a high milk-to-plasma ratio. Increased postnatal loss and suppressed postnatal development were observed in rats at 150 mg/kg/day in the diet, equivalent to about 55x the human exposure, based on AUC. Since it may also be excreted in human milk, Zelmac should not be prescribed to women who are breast-feeding.

INTERACTIONS
Specific in vitro drug-drug interaction studies with theophilline (CYP1A2 prototype substrate), dextromethrophan (CYP2D6 prototype substrate), digoxin, warfarin, and oral contraceptive indicated no clinically relevant interactions. No dosage adjustment is required when tegaserod is coadministered either with drugs metabolised by CYP2D6 (e.g. fluvoxamine, captopril, omeprazole), or with digoxin, warfarin or oral contraceptives.

During the tegaserod clinical studies, no clinically relevant drug-drug interaction was identified in patients who concomitantly used selective serotonin reuptake inhibitors, tricyclic antidepressants, oral contraceptives, proton pump inhibitors or $H_2$ blockers.

ADVERSE REACTIONS
Adverse Events Reported in Clinical Trials
In placebo-controlled studies of 2446 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.

GI disorders were the most frequently reported AEs; and occurred more frequently with tegaserod than with placebo. The next most common AEs were those of the central and peripheral nervous system and general disorders.

In Pooled Phase 3 studies (see Table 2), diarrhoea was reported as an adverse event by 8,8% of patient treated with tegaserod 6 mg twice a day, whereas the corresponding figure for placebo was 3.8%. In most cases diarrhoea occurred early, was transient, most often observed as a single episode during 12-week treatment period, and resolved with a continued therapy. The rate of discontinuation from the studies due to the diarhoea was low with 1.5% in tegasterod-treated patients. The frequency of most other adverse events was similar in tegaserod and p;acebo-treated patients.

Table 2: Adverse events in ³ 1% 0f patients on Zelmac in double-blind Phase III studies

| Body system | Zelmac 6 mg BID | Placebo |
|---|---|---|
| | (n=1327) | (n=1305) |

| | | |
|---|---|---|
| **Gastrointestinal system disorders** | | |
| Abdominal pain | 11.5 | 10.9 |
| Diarrhoea | 8.8 | 3.8 |
| Nausea | 8.1 | 6.7 |
| Flatulence | 6.3 | 4.8 |
| Dyspepsia | 4.2 | 3.8 |
| Vomiting | 2.3 | 2.7 |
| Gastroenteritis | 2.2 | 2.2 |
| Constipation | 1.1 | 1.6 |
| Tooths disorders | 1.1 | 1.2 |
| Haemorrhoids | 1.1 | 0.7 |
| **Central and peripheral nervous system** | | |
| Headache | 15.0 | 12.3 |
| Dizziness | 3.8 | 3.4 |
| Migraine | 1.5 | 1.1 |
| **Body as a whole- General disorders** | | |
| Influenza-like symptoms | 4.0 | 3.8 |
| Accidental trauma | 2.6 | 1.8 |
| Fatigue | 2.3 | 2.0 |
| Chest pain | 1.3 | 0.8 |
| Pain | 1.2 | 1.3 |
| Allergy | 1.0 | 0.9 |
| Fever | 1.1 | 1.2 |
| Oedema Peripheral | 1.1 | 0.6 |
| **Respiratory system disorders** | | |
| Upper resp. tract infection | 4.1 | 7.1 |
| Sinusitis | 3.3 | 3.9 |
| Pharyngitis | 2.3 | 2.6 |
| Rhinitis | 1.8 | 1.8 |
| Coughing | 1.2 | 1.8 |
| Bronchitis | 1.4 | 1.9 |
| **Musculo-skeletal systems disorders** | | |
| Back pain | 4.8 | 4.1 |
| Arthropahty | 2.0 | 1.0 |
| Myalgia | 1.1 | 0.8 |
| **Skin and Appendages disorders** | | |
| Rash | 1.0 | 1.8 |
| **Urinary system disorder** | | |
| Urinary tract infection | 3.1 | 3.1 |
| **Reproductive disorders, female** | | |
| Dysmenorrhoae | 1.4 | 1.1 |
| Moniliasis genital | 1.2 | 1.6 |
| **Psychiatric disordes** | | |
| Insomnia | 2.2 | 2.0 |
| Anxiety | 1.1 | 1.1 |
| **Hearing and vestibular disorders** | | |
| Otitis media | 1.0 | 0.6 |

The respective frequency of surgical interventions for tegaserod (n=2965) and placebo (n=1740) were: abdominal surgery 0.30% (n=9) vs 0.17% (n=3), p=0.37; cholesystectomy 0.16% (n=5) vs 0,06% (n=1), p=0.22; pelvic 0.13% (n=4) vs 0.23% (n=4), p=0.71.

Uncommon (>1/1000, <1/100) adverse events were (% Zelmac vs % Placebo); Bronchoplasm (0.5 vs 0.1), granulocytopenia (0.7 vs 0.2), faecal incontinuence (0.5 vs 0.2), urinary incontinence (0.5 vs 0), and appetite increase (0.5 vs 0).

OVERDOSE

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

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.

PHARMALOGICAL PROPERTIES

Pharmacodynamics

Tegaserod is a serotonin type-4 receptor (5- HT4) partial agonist. It binds to 5- HT4 receptors and has little affinity for 5-$HT_3$ or dopamine receptors. Tegaserod stimulates gastrointestinal motility and intestinal peristaltic reflex, and inhibits intestinal sensitivity via activation of 5-$HT_4$ receptors in the gastrointestinal tract. *In vivo* studies in animals showed that tegaserod enhanced basal motor activity and normalize impaired motility of the gastrointestinal tract.

Pharmacokinetic

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

Absorption

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%. $T_{max}$ of tegaserod was 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 meal.

The pharmacokinetics were dose proportional over the range of 2 mg to 12 mg tegaserod given twice daily for 5 days. There was no clinically relevant accumulation of tegasterod in plasma when 6 mg was given twice daily for 5 days.

Distribution

Tegaserod is approximately 98% bound to plasma proteins, primarily to $a_1$-acid glycoprotein. It is extensively distributed into tissues following intravenous administration, with a volume of distribution at steady state of 368 ± 2231.

Metabolism

Tegaserod has two main metabolic pathways. The first involves presystemic acid-catalyzed hydrolysis in the stomach, followed by oxidation and conjugation, resulting in the main metabolite of tegasterod, 5-methoxy-indole-3carboxylic acid glucuronide. The main metabolite has negligible affinity for 5-$HT_4$ receptors. In man, there was no statically 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 isoenzyme CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4, whereas inhibition of CYP1A2 and CYP2D6, could not be excluded and was therefore studied *in vivo*. (see Precaution, interactions with other drugs). The main human metabolite did not inhibit the activity of any of the above cytochrome P450 isoenzymes.

Elimination

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 faeces, with the remaining one-third excreted in the urine, primarily as the main metabolite.

Pharmacokinetics in the elderly

Elderly: The Pharmacokinetics of tegaserod were similar between elderly males and young males, whereas the mean AUC and $C_{max}$ are 40% and 22%, greater in the elderly females than in young females but still within the variability seen in the healthy subjects. Therefore, dose adjustment in elderly patients is not necessary.

Pharmacokinetics in patients with hepatic impairment

In subjects with mild to moderate hepatic impairment, mean AUC was 43% higher and $C_{max}$ 18% higher compared to subjects with normal hepatic function. No dosage adjustment is required in patients with mild to moderate hepatic impairment, however, caution is recommended when using tegaserod in this patient population. ZELMAC has not

been studied in patients with severe hepatic impairment, and is therefore not recommended in these patients.

Pharmacokinetics in patients with renal impairment
No change in the pharmacokinetics of tegaserod was observed in subjects with severe renal impairment requiring haemodialysis (creatinine clearance £15 ml/min/1.73m$^2$). $C_{max}$ and AUC of the main pharmacologically inactive metabolite of tegaserod, 5-mothoxy-indole-3-carboxyclic acid glucoronide, 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. Zelmac is not recommended in patients with severe renal impairments.

Clinical trials
The efficacy of Zelmac in females with constipation predominant IBS was established in two prospective well-controlled studies (B301 and B358) of 12 weeks duration with supportive efficacy obtained from a subgroup analysis of females in study B351. In study B301, efficacy was established in a subgroup analysis of female patients (n=275) while study B358 enrolled only female subjects. Study B351 which showed consistently favourable results for tegaserod was used to prospectively define the primary endpoints for studies B301 and B358. The results of study B351 were largely confirmed and replicated in studies B301 and B358. A subgroup analysis of female patients in fourth study (Study B307) did not demonstrate a statically significance difference in efficacy between tegaserod and placebo. From the three clinical studies which included male subjects, efficacy in males could not be established. Results from the four clinical studies are summarized in table1.

Table 1: Responder rates in female patients at end point

| Study | Responder Rate (n) | | p-value |
|---|---|---|---|
| | Tegaserod 12 mg/day | Placebo | |
| B301 | 38.9% (244) | 27.5% (240) | 0.008 |
| B307* | 42.9% (233) | 37.6% (234) | 0.242 |
| B351 | 47.4% (234) | 33.2 (235) | 0.002 |
| B358 | 43.5% (767) | 38.8 (752) | 0.033 |

* Patients in Study B307 were initially treated with 4mg/day and titrated up to 12 mg/day after 4 weeks

In the largest study, (B358), 1,519 women with IBS with contipation were randomised in a double-blind manner to either 6mg twice a day Zelmac or Placebo for 12 weeks. Patients were selected based on Rome criteria and had to fulfil 2 or 3 constipation criteria (<3 bowel movement per week, hard stool or straining).
Patients rated their weekly response using the Subject's Global Assessment (SGA) of Relief, a 5 level categorial scale (completely relived, considerable relieved, somewhat relieved, unchanged, worse), which took into account their overall well-being, symptoms of abdominal pain/discomfort and altered bowel function. Overall responder rates at endpoint were 43.5% (Zelmac) vs 38.8% (Placebo); p=0.033. The (p=0.006) and 5.9 % (p=0.025). In addition, Zelmac produced significant improvement in the SGA of abdominal pain and SGA of statisfaction with bowel habits. These effects were seen within the first week, were most pronounced in the initial 4-6 weeks and maintained throughout the treatment period. Daily bloating scores were significantly (p<0.005 improved during the first 7 weeks of the study. Significant improvement in the 3 bowel-related assessments (stool frequency, stool consistency and straining) were observed within the first week and sustained throughout the treatment.

Overall, Zelmac at a dose of 6 mg twice a day showed a consistent pattern of improvement in studies B301, B351 and B358. Higher response rates were observed for the Zelmac-treated group than the placebo group on SGA of Relief for each month in all three studies (8 of 9 months, $p < 0.05$). In particular, Zelmac had a rapid onset of action with a therapeutic gain in month 1 of 11-13% over placebo. A Study endpoint, the therapeutic gain ranged from 5-12%. Zelmac-treated patients also showed greater improvements than placebo-treated patients also showed greater improvements than placebo-treated patients in the important symptoms of IBS, including abdominal discomfort and pain, bloating and symptoms of constipation.

**EXCIPIENTS**
Crospovidone, Glyceryl monostearate, hypermellose, lactose monohydrate, poloxamer 188, macrogol 4000.

**INCOMPATIBILITIES**
Not applicable

STORAGE

Store below $30^0$C. Store in the original package. Medicines should kept out of the reach of the children.

**HARUS DENGAN RESEP DOKTER**

**PACKAGE QUANTITIES AND REGISTRATION NUMBER**

ZELMAC 6mg tablets: box of 1 blisters @ 10 tablets Reg. No….
Box of 3 blisters @ 10tablets Reg. No….

Manufactured by Novartis Pharma AG, Switzerland,
Imported by PT Novartis Biochemie, Citereureup, Bogor, Indonesia