European Medicines Agency
Evaluation of Medicines for Human Use

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Refusal Assessment Report

For
ZELNORM

International Nonproprietary Name:
TEGASEROD

Procedure No. EMEA/H/C/621

This Assessment Report is the CHMP Assessment Report with all commercially confidential information removed.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novartis Europharm Limited submitted on 29 September 2004 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Zelnorm, through the centralised procedure.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application, (i.e. complete dossier with administrative, quality, non-clinical and clinical data).

The application submitted is a complete dossier:

composed of administrative information, complete quality data, non-clinical and clinical data based on applicant's own tests and studies.

The applicant applied for the following indication: Zelnorm is indicated for the repeated symptomatic short-term treatment of Irritable Bowel Syndrome in women whose predominant bowel habit is constipation (IBS-C).

Licensing status:
Zelmac has been given a Marketing Authorisation in the following countries:

Lichtenstein, Australia, Canada, USA, South Africa, Switzerland, Albania, Argentina, Aruba, Bahrain, Bangladesh, Brazil, Chile, China, Columbia, Costa Rica, Curacao, Dominican republic, Ecuador, Egypt, El Salvador, Guatemala, Honduras, Hong Kong, India, Indonesia, Israel, Jamaica, Korea, Kuwait, Lebanon, Malaysia, Morocco, Mexico, New Zealand, Nicaragua, Pakistan, Palestine, Panama, Peru, Philippines, Romania, Russia, Singapore, Taiwan, Tanzania, Thailand, Trinidad, Turkey, Ukraine, UAE, Uruguay, Venezuela, Vietnam, Yemen & North Fed. Rep. Yugoslavia

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Dr Tomas Salmonson

Co-Rapporteur: Dr Gonzalo Calvo Rojas

1.2 Steps taken for the assessment of the product

- The application was submitted to the EMEA on 29 September 2004.
- The procedure started on 18 October 2004.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 23 December 2004. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 29 December 2004.
- During the meeting on 14-17 February 2005, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 February 2005.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 8 July 2005.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 August 2005.
- During the CHMP meeting on 12-15 September 2005, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and in an oral explanation by the applicant.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 November 2005.
- During the CHMP meeting on 14-17 November 2005, outstanding issues were addressed by the applicant during an oral explanation before the CHMP on the 16 November 2005.
- During the CHMP meeting on 16 November 2005 an Expert group was convened to address questions raised by the CHMP.
- During the meeting on 12-14 December 2005, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for Zelnorm.

1.3 Steps taken for the re-examination procedure

- The applicant submitted written notice to the EMEA on 22 December 2005 to request a re-examination of the Zelnorm CHMP opinion of 14 December 2005.
- During its meeting on 20-23 January 2006, the CHMP appointed Dr Eric Abadie as Rapporteur and Dr Steffen Thirstrup as Co-Rapporteur for the re-examination procedure.
- The detailed grounds for the re-examination request were submitted by the applicant on 17 February 2006. The re-examination procedure started on 18 February 2006.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 6 March 2006. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 3 March 2006.
- An Ad hoc Expert Group meeting on Zelnorm was held on 15 March 2006 at the EMEA. During this meeting the applicant presented an oral explanation. A report of this meeting was forwarded to CHMP.

- During the CHMP meeting on 20-23 March 2006, the applicant presented an oral explanation before the CHMP on the 21 March 2006.

- During the meeting on 20-23 March 2006, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final Opinion recommending the refusal of the granting of the Marketing Authorisation for Zelnorm.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Irritable Bowel Syndrome (IBS) is a functional disorder of the gastrointestinal tract (GIT) characterized by abdominal pain/discomfort, bloating and altered bowel function. IBS is common and may have a significant impact on a patient's quality of life. Psychological symptoms are common. The prevalence of IBS is up to 20%; 14-25% of women and 5%-19% men (N. J Talley et al; 1992). The female to male ratio varies 1.1-2.6 depending on the predominant symptom; constipation is commoner in women whereas men may have a tendency to diarrhoea (N. J Talley et al; 1995).

Tegaserod, an aminoguanidine indole compound is a potent, orally active $5HT_4$ agonist with high affinity, which acts on enteric nerves in the gastrointestinal tract to trigger the release of neurotransmitters, resulting in increased gastrointestinal contractility and stimulation of the peristaltic reflex. Because of its pharmacological action at $5HT_4$ receptors in the gut, tegaserod was expected to improve the characteristic symptoms of abdominal discomfort and pain, bloating and constipation that occur intermittently but recurrently in IBS-Constipation (IBS-C).

The applicant Novartis Europharm Limited submitted a complete and independent application for Zelnorm (tegaserod) according to article 8.3 of Directive 2001/83/EC, as amended.

The indication proposed by the applicant for Zelnorm was: '*repeated symptomatic short-term treatment of Irritable Bowel Syndrome in women whose predominant bowel habit is constipation (IBS-C).'*

The recommended dose of Zelnorm was one 6 mg tablet twice daily.

2.2 Quality aspects

Introduction

Each tablet of Zelnorm contains 6 mg tegaserod, as the hydrogen maleate. The tablet formulation may be described as standard, and modified-release was not considered necessary. The proposed packaging was PVC/PE/PVDC blister packs.

Active Substance

The solubility of tegaserod hydrogen maleate was found to be low in all tested solvents, especially so in water and all aqueous buffer solutions, where the solubility is very low and the addition of surfactants only slightly increased the solubility. Tegaserod hydrogen maleate is not optically active and was present as a thermodynamically stable physical form in the tablet formulation.

- Manufacture

Tegaserod is a chemically-synthesised substance.

- Specification

The specifications for the active substance were set in line with the batch data and ICH requirements. The batch results show good consistency and all methods have been acceptably described and validated.

- Stability

The active substance was found to be stable and all results remained within specifications under long term storage conditions and up to 6 months under accelerated storage conditions. An acceptable and valid re-test period was defined.

Medicinal Product

- Pharmaceutical Development

Because of the very low water solubility of the drug substance, the particle size distribution has been determined routinely as it may influence the dissolution behavior. Because the drug substance is rapidly absorbed after oral administration, and due to its physico-chemical properties, oral formulations were preferred. Initially a capsule formulation was developed and later 2mg and 6 mg tablet formulations were developed.

- Manufacture of the Product

The results from the validation of the manufacturing method together with the results of the in process controls and of the release analysis demonstrated that the manufacturing process of Zelnorm 6 mg tablets was robust and consistently yields a product which meets all agreed quality characteristics.

- Product Specification

The test methods have been acceptably described and have been validated according to the ICH guidelines. The proposed release and shelf life specifications have been justified and batch results complied with the specifications and agreed quality criteria.

- Stability of the Product

Based on the stability data provided, and the current EU/ICH guidelines an acceptable and validated shelf-life was defined, together with recommended storage conditions.

Discussion on chemical, pharmaceutical and biological aspects

The manufacture and control of the active substance and finished product have been evaluated and judged to be satisfactory for a product of this type.

2.3 Non-clinical aspects

Introduction
The pivotal toxicity studies, including toxicokinetics were conducted in accordance with GLP.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

Tegaserod has high affinity for the human 5-HT_4 receptor (pK_d: 7.7). In guinea-pig ileum preparations, it acted as a partial agonist. One main human metabolite, M29 had no appreciable 5 HT_4 binding. Data for metabolite 52.8 indicated that it was more potent than tegaserod. However this metabolite is not detected in human plasma, and present in rodents at low levels only. Therefore as argued by the Applicant, it was agreed that even if this metabolite has similar or higher pharmacological activity than tegaserod, it is of no clinical relevance. Other human metabolites include three isomeric metabolites M43.2, M43.8 and M45.3, which are N-glucuronidates of tegaserod. Further pharmacological testing of these metabolites has not been undertaken.

In vitro and *in vivo* experiments showed that tegaserod increased motility and tone in the GIT. The dose-response curve appeared bell-shaped, which makes dose-response interpretations difficult. Published data on *in vitro* preparations of GI tissues showed that tegaserod led to the release of various transmitters e.g. calcitonin gene-related peptide (CGRP), substance P and vasoactive intestinal peptide (VIP). It also increased intracellular concentrations of cyclic AMP. In various *in vivo* models, tegaserod accelerated the gastric emptying of solids in both rats and dogs, but had no effect on the inhibition of gastric emptying of solids induced by light colonic distension. There was an indication of antinociceptive activity during colorectal distension in rats. In dogs, tegaserod normalised morphine-induced constipation.

- Secondary pharmacodynamics

Experiments on the general human receptor profile of tegaserod showed that it has high affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2B} receptors (pK_i: 7.2-8.1) - comparable to its 5-HT_4 affinity. Functional experiments revealed tegaserod as being a partial 5-HT_{1A} agonist and a competitive 5-HT_{1B} and 5-HT_{2B} antagonist. It had weak or no relevant affinity (pK_i <6.5) for all other binding sites tested.

- Safety pharmacology

Safety pharmacology testing addressing cardiovascular safety (*in vitro* hERG channel, papillary muscle cells, isolated rabbit heart; *in vivo* studies in rats and dogs), gastric acid secretion and renal function revealed no cause for concern. In a new set of studies it was shown that overall, tegaserod appeared to have no vasoconstrictive potential. Tegaserod showed some reduction in prolactin secretion in rats. The applicant claims that tegaserod is devoid of CNS effects at therapeutically relevant doses, but findings in mice safety pharmacology studies suggest certain CNS related effects such as increased activity, abnormal gait, hypothermia at 10 to 100-fold higher doses.

- Pharmacodynamic drug interactions

No non-clinical studies have been undertaken.

Pharmacokinetics
A comprehensive set of pharmacokinetic studies has been undertaken with tegaserod, in the species used for toxicity testing. The methods used for the analyses of tegaserod and metabolites in plasma, tissues and excreta were validated and adequate overall.

- Absorption- Bioavailability

In all species, the degree of absorption was <35 %, and the absolute bioavailability between 8-27%. The oral absorption rate was moderate to fast, with a T_{max} of 0.5-5 h in animals. The plasma clearance of tegaserod was higher in rodents than in dog and human, which resulted in lower dose-normalised AUCs in rodents (1-18) than in dog (60-200) and human (40-80). Terminal half-lives of tegaserod

(i.v.) were 2.1 h in rodents, 8.6 h in dogs, while half-lives of plasma radioactivity were substantially longer (30- 75 h).

- Distribution

The plasma protein binding of tegaserod was high in all species (95-98%). Studies in albino and pigmented rats showed widespread distribution of radioactivity. A high degree of labelling was seen in GIT, liver, kidney, adrenal, brown fat and thyroid. In pigmented rats, significant uptake and retention in melanin containing tissues were observed.

In specific studies on CNS distribution, low brain uptake was seen in normal rodents (brain/plasma ratios 0.075-0.36). The role of P-glycoprotein (P-gp), an ATP-dependent efflux transporter was also investigated. It was found that tegaserod increased 4-10 fold in knock-out mice lacking brain P-gp These data confirm that tegaserod is transported by the P-gp efflux pump. This finding may be important in terms of drug interactions, which is further addressed in the Clinical section.

Studies of placental transfer in rats and rabbits showed that radiolabeled product crossed the placenta. The amnion:maternal blood ratio was >5, while the fetal:maternal blood ratio was low (<0.2). In rats, foetal clearance was slower than from maternal tissues, and foetuses were exposed mainly to metabolites. In rats, $AUC_{0\text{-}24\ h}$ for radioactivity and tegaserod was 3 times and 20 times higher in milk than in plasma respectively.

- Metabolism (*in vitro/in vivo*)

The metabolism of labelled tegaserod was investigated in the mouse, rat, rabbit, dog and humans. In all species, tegaserod was only a minor part of the AUC radioactivity in plasma after oral dosing. Four main metabolic (or degradation) pathways were characterized. The *first* involved hydrolytic cleavage in the stomach to pentylaminoguanidine (PAG) and an aldehyde, which further underwent oxidation to M38.0 and subsequent conjugation to M7.0 or M29.0. They were the major metabolites in plasma after oral administration in all species. The *second* pathway consisted of direct N-glucuronidation of tegaserod, to three isomeric metabolites (M43.2, M43.8 and M45.3). They were detected in all species except the dog. The *third* pathway involved O-demethylation of tegaserod (to M52.8), followed mainly by glucuronidation (M40.6). This pathway was important in rodents, minor in dogs and undetectable in humans *in vivo*, but human liver microsomes formed M52.8. A *fourth* pathway, consisted of oxidations in the indole substructure and subsequent conjugations, and was seen mainly in the rat.

The fate of PAG was studied specifically in mice. The possibility that nitroso derivatives of PAG could be formed, posing a genotoxic risk, was discussed. It is agreed with the applicant that a genotoxic risk due to reaction of PAG with nitrite in the stomach is judged as negligible.

- Excretion

Excretion of radioactivity was mainly via feces, while urine contained 8-25% of the dose (almost no unchanged tegaserod) in rodents and dogs.

Toxicology

Rat, mouse, dog and rabbit were the main species used for toxicity testing. Exposure to all identified human metabolites appears to have been achieved in at least one species used in the respective toxicology studies, and these species are therefore considered relevant models for safety testing.

- Single dose toxicity

Single gavage dosing in mice was lethal at low doses (100 mg/kg), and therefore dietary dosing was used for repeat dose studies in rodents.

- Repeat dose toxicity (with toxicokinetics)

The repeat dose toxicity of tegaserod was carried out in mice, rats and dogs (capsule).

In mice, tegaserod mortalities occurred at 900 mg/kg/d for 13 weeks. Mucosal hyperplasia was seen in

the small intestine after 2 weeks (400 mg/kg/d).

In rats (26 weeks), and dogs (52 weeks), no organ toxicity was observed. Reduced body weight (BW) gain and food intake, and some clinical signs were seen in both species at the high doses tested (240 and 60/70 mg/kg/d, respectively). The NOEL (no observed effect level) was 60 mg/kg/d in rats and 15 mg/kg/d in dogs, with systemic exposures being 7-11 times or 100 times higher than the clinical exposure. There were certain indications of hepatic effects (altered enzyme activities with no histopathological correlates in mice and dogs; slight histopathological alterations with no enzyme changes in rats). However, overall there was no clear indication of hepatotoxicity.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

The genotoxic potential of tegaserod was studied *in vitro*, in assays on bacterial mutations (Ames test), and clastogencity (HGPRT locus and chromosome aberration tests in V79 cells) and *ex vivo* (unscheduled DNA synthesis test in rat hepatocytes). Two *in vivo* studies in mice were undertaken at the maximum tolerated dose (MTD); a bone marrow micronucleus test and a Comet assay, with tissues from the jejunum and liver (doses as in carcinogenicity study). Overall, there was no indication of genotoxic effects.

- Carcinogenicity (with toxicokinetics)

Carcinogenicity was tested in CD-1 mice dosed for 104 weeks and Wistar rats dosed for 110-124 weeks, via the diet. The MTD was reached in both species. The validity of both studies, as well as a 13-week mechanistic study in mice (971076), was seriously questioned due to the presence of small amount of drug in the plasma of a few control animals. After further clarification, it was concluded that the rat study was valid.

The applicant was also asked to address findings of haemangioma/sarcoma in the rat study. It was concluded that there was no indication of carcinogenicity in rats dosed for 2 years with tegaserod, at exposure levels 130 times above clinical exposure.

In mice, no convincing explanation for the presence of small amount of drug in the plasma of a few control animals was found. Nevertheless, the CPMP[1] advised that repetition of the 2-year mouse study may not be needed, if adequate mechanistic data were provided. As outlined below, the applicant has submitted new mechanistic studies.

In the mouse carcinogenicity study, adenocarcinomas were found in the small intestine of 8 animals (7 in jejunum, 1 in ileum) from the high dose group (600 mg/kg/d), as well as mucosal hyperplasia. Mucosal hyperplasia of intestinal tissues was also found in other studies of shorter duration (see section on Repeat dose toxicity).

It had been hypothesized initially that inhibition of diamine oxidase (DAO) could be involved in mechanisms triggering intestinal hyperplasia and neoplasia in mice. However, although tegaserod appeared to inhibit DAO activity both after acute and repeated administration, no alteration of polyamine levels in plasma, urine or intestinal tissues was identified after a single dose or up to 13 weeks dosing. Therefore the data provided did not support this proposed mechanism as solely being responsible for the observed tumours in mice.

The possibility that the interaction of tegaserod with 5-HT receptors was involved in the hyperplastic response was raised. The applicant undertook a set of studies, which showed that stimulation of 5-HT_4 or 5-HT_{1A} receptors was not involved in the intestinal hyperplasia induced by tegaserod.

Another series of studies provide a reasonable mechanistic explanation for the intestinal tumours observed in the mouse carcinogenicity study. It appears that high doses of tegaserod cause cellular stress, and that the sensitivity of human and mouse tissues was comparable in this respect. Such stress

[1] The CHMP (Committee for Human Medicinal Products) was previously known as the CPMP (Committee for Proprietary Medicinal Products) prior to June 2004.

may trigger a proliferative response in the intestinal mucosa, resulting in mucosal hyperplasia and upon lifetime treatment this hyperplasia is sustained in some mice, resulting in subsequent tumour formation. It is apparent that a tumour risk does not exist at doses that do not induce hyperplasia. These additional data also better support that the hyperplastic response was due to local tegaserod exposure. At the NOEL (150 mg/kg in mice); the margins are 18-fold for systemic exposure (AUC) and several 100-fold for local exposure (dose comparisons). These margins are considered sufficiently large to conclude that the finding of intestinal tumours in mice is not of concern for the intended clinical use of tegaserod.

- Reproductive and developmental studies

A standard series of reproduction and developmental toxicity studies were conducted by oral gavage in rats and rabbits (segment II only). Marked toxicity, and high mortality due to the gavage administration, limited the value of the rat studies. Therefore, in total four diet studies were undertaken, where tegaserod was considerably better tolerated, despite that higher systemic exposures were achieved.

Female fertility and general reproductive performance (dosing 14 days before mating to gestation day 20 or lactation day 21) were studied in one gavage and one diet study, and two mechanistic gavage studies. These studies showed evidence for impaired implantation and early embryonic development, as well as reduced pup survival. Possible NOELs are 75 mg/kg/d (diet) or 6 mg/kg/d (gavage). However, exposure margins are uncertain due to the presence of small amounts of drug in the plasma of a few control animals in the diet study and since tegaserod was not detected in plasma at 6 mg/kg/d (gavage). Hence the use of tegaserod in women attempting to conceive should be restricted.

No effects on male fertility were identified after gavage or diet dosing 9 weeks before and throughout mating, despite severe toxicity in the gavage study.

Peri-post natal development was studied in four diet studies of various designs. One also included a juvenile development part. In all studies, decreased F_1 pup weights, and increased pup mortality were noted during weaning, possibly due to exposure during pregnancy, via milk and /or the diet. Based on the totality of data, the NOEL for the F_1 generation is 25 mg/kg/d; a dose for which no systemic exposure to tegaserod was demonstrated in either dams or offspring. At the LOEL (lowest observable/observed effect level) for pup mortality, the systemic exposure of dams was less than 2 times the clinical exposure. Delayed sexual development, effects on various other developmental endpoints and reduced body weight were also seen. Thus, women who breast feed should not be treated.

Concerns were raised whether tegaserod altered endocrine function, due to the effects on early embryonic development /implantation parameters in rats, delayed sexual development in F_1 offspring (testis descent, vaginal opening), findings of ovarian cysts in tegaserod treated females in the rat carcinogenicity study, and effects on hormones. Decreased prolactin (Gestation Day 3), and reduced estradiol (Gestation Day 21) were observed, which may both be toxicologically relevant. However, data from another study revealed no hormonal effects. Thus, the overall effect of tegaserod on hormones remains unclear. Additional argumentation by the applicant has not provided further clarification. However, the data are not clear-cut, and anti-androgenic effects were not evident in all studies. Thus, the anti-androgenic potential of tegaserod, if any, is weak although such a risk cannot be excluded completely. Nevertheless, it supports the conclusion that the use of tegaserod during pregnancy should be avoided.

In juvenile rats, additional noteworthy findings included some effects on organ weights and microscopic thyroid changes at high dose. The NOEL for juvenile animals was 75 mg/kg/d ($AUC_{0\text{-}24\ h}$ of 250 ng*h/ml).

Segment II gavage studies were undertaken in rats and rabbits. In rats, maternal toxicity and mortality occurred, while no clear maternal toxicity was seen in rabbits. Embryotoxicity (retarded embryo/foetal development) was observed in both species, without teratogenic effects. In rats, the maternal and developmental NOELs resulted in exposure margins of 8 or 30 times the clinical exposure. In rabbits,

embryotoxicity was observed in all treated groups, with systemic exposure at the lowest dose 6 times higher than the anticipated clinical exposure. It was concluded that the use of tegaserod during pregnancy should be avoided.

- Local tolerance

Repeat dose toxicity studies with i.v. infusion indicate that tegaserod has an irritant potential via the i.v. route. Data from sensitization models suggest that it has a low skin sensitization potential.

- Other toxicity studies

Data from distribution studies indicate that tegaserod does bind to melanin. Tegaserod absorbs light in the UVA/B range and in the infrared region, within the wave-length range indicated in the Note for Guidance on Phototoxicity Testing CPMP/SWP/398/01. The applicant has undertaken a new study the 3T3 NRU PT assay, which shows that tegaserod is devoid of phototoxic potential. In addition the recently submitted data from the *in vitro* Comet assay addressing photogenotoxicity does not raise any concern.

Relevant impurities have been adequately qualified by their presence in pivotal toxicity studies.

Ecotoxicity/environmental risk assessment

Acute studies had already been performed according to the regulatory requirements at the time of submission, no chronic studies were performed for animal welfare reasons and because PEC/PNEC ratios based on acute studies using assessment factors up to 100,000 indicated no relevant risk.

All Phase II Tier A studies using unlabelled material have been performed, including an OECD 121 study. No chronic studies have been performed, since risk ratios based on already acquired acute data indicate no concern, even when using assessment factors up to 100,000 and references (in Kiefer 1999). In addition, data on dissociation constant in water (OECD 112), spectral analysis UV-VIS (OECD 101) and melting temperature (OECD 102) are available.

The adsorption - desorption study in soil (OECD 106) was ongoing during the procedure.

2.4 Clinical aspects

Introduction

According to the applicant, all clinical studies were conducted in full compliance with the principles of Good Clinical Practice. All studies were closely monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.

Table 1 - Summary of placebo controlled studies to demonstrate efficacy in the proposed indication

Study No.	Study objective, population	Patients randomized	Treatment duration	Medication dose/day	Primary efficacy variable (timepoint, scale)
1 key study (2 primary outcome variables, 4 weeks repeated treatment)					
A2306	efficacy/safety and repeated treatment in IBS-C *women*	2660	4 wks + 4 wks re-treatment	placebo, 6 mg bid tegaserod	1) Relief of overall IBS symptoms (wks 1-4, binary scale) 2) Relief of abdominal discomfort/pain (wks 1-4, binary scale)
5 supportive studies					
2 studies with binary efficacy scale					
AFI01	efficacy/safety in non D-IBS *women & men*	647	12 wks	placebo, 6 mg bid tegaserod	relief of overall IBS symptoms (first 4 wks, binary scale)
ASG01	efficacy/safety in non D-IBS *women & men*	520	12 wks	placebo, 6 mg bid tegaserod	relief of overall IBS symptoms (first 4 wks, binary scale)
3 studies with ordinal efficacy scale					
B301	Efficacy, safety, and dose-response in IBS-C *women & men*	881	12 wks	placebo, 2 or 6 mg bid tegaserod	Relief of overall IBS symptoms[1] (last 4 wks, ordinal scale)
B351	Efficacy, safety, and dose-response in IBS-C *women & men*	799	12 wks	placebo, 2 or 6 mg bid tegaserod	Relief of overall IBS symptoms[1] and intensity of abdominal discomfort/pain[2] (last 4 wks, ordinal scale)
0358	Efficacy/safety study in IBS-C *women*	1519	12 wks	Placebo, 6 mg bid tegaserod	Relief of overall IBS symptoms[1] (last 4 wks, ordinal scale)

IBS-C = irritable bowel syndrome with constipation, non D-IBS = non diarrhoea-predominant irritable bowel syndrome, wks = weeks, SGA = Subject's Global Assessment
[1] originally called SGA of relief of IBS symptoms
[2] originally called SGA of abdominal discomfort/pain (visual analogue scale)

Pharmacokinetics

- Absorption

After oral administration, tegaserod is rapidly absorbed with a median T_{max} of 1 h. The absolute bioavailability is about 10 % under fasting conditions. The absorption is potentially P-glycoprotein and pH-dependent.

A total of 5 oral formulations (2 capsules and 3 tablets) were used during the clinical development of Zelnorm. All phase III efficacy trials were performed with the same tablet formulation, the so-called final market image (FMI tablet), which was not the formulation eventually intended for marketing.

A new tablet formulation of Zelnorm (new FMI tablet) has been developed with a different qualitative and quantitative composition and similar *in vitro* dissolution profiles that is manufactured by direct compression (DC), instead of wet granulation (WG). A bioequivalence study was performed to compare the new FMI tablet to the former FMI tablet used in phase III studies. The formulations were found to be bioequivalent with respect to AUC. For C_{max}, the mean ratio and 90% confidence interval were 0.87 (0.79-0.97). The difference in C_{max} between the new FMI tablet and the "initial" FMI tablet is considered to lack clinical relevance, based on the relatively flat dose response relationship between 2 mg bid and 12 mg bid.

C_{max} and AUC were reduced by 69 and 67%, respectively when the new FMI tablet was administered with food. A significant food effect has been observed, also with other formulations (the DSF capsule and the FMF tablet), with a reduction in the rate and extent of tegaserod absorption by 40-55 % for AUC0-∞ and 20-40 % for C_{max}. The effect of food on the "initial" FMI tablet was not studied. It was recommended to take tegaserod orally before a meal. Phase III efficacy trials were performed according to this dosing recommendation.

- Distribution

Tegaserod has a relatively high volume of distribution at steady state of 368 ± 223L (after i.v. administration). The 20-fold decrease in plasma concentration within 1 h after termination of the i.v. infusion suggests that distribution is rapid. In human plasma, the fraction bound was approximately 98 %, mainly to α1-acid glycoprotein. In concentrations exceeding those of the parent drug, metabolite M 29.0 does not displace tegaserod from its binding sites.

The potential role of P-glycoprotein (P-gp) in CNS penetration of tegaserod was further investigated. As P-gp is an ATP-dependent efflux transporter expressed in the blood-brain barrier, the transport may limit CNS distribution of tegaserod. This was also supported by the findings in mdr-1-knockout mice. The quantitative role of P-gp is at present unknown. It cannot therefore be excluded that the CNS distribution of tegaserod increases in the presence of an inhibitor of P-gp in man.

- Elimination

The plasma clearance of tegaserod is 77 ±15 L/h, with an estimated terminal half-life ($t_{1/2}$) of approximately 11 hours following i.v administration. The variability in exposure during oral administration (C_{max} and AUC) appears to be about ±50%.

The metabolism of tegaserod is somewhat unclear. Tegaserod is metabolised 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-methoxy-indole-3-carboxylic acid glucuronide (M29.0). In man, systemic exposure to tegaserod was not statistically significantly altered at neutral gastric pH values. The second metabolic pathway of tegaserod degradation is direct glucuronidation, which leads to generation of three isomeric N-glucuronides. The metabolite to parent drug plasma concentration (C_{max}) ratio is approximately 19 and 10 for M29.0 and M7.0, respectively. It may not be excluded that tegaserod also is partly eliminated by biliary secretion.

Unchanged tegaserod accounts for only few percent of total radioactivity in plasma. The predominant compound in plasma is the metabolite M29.0. The majority of the radioactively labelled compounds are excreted in the faeces (58 %, mainly as unchanged tegaserod) and 27 % in urine (mainly as metabolite M29.0, no unchanged tegaserod). Total recovery of the dose is 85 % within 168 h.

The main metabolite, as expected, has negligible affinity for 5-HT_4 receptors.

- Dose and time-dependencies

The pharmacokinetics (PK) of tegaserod is dose proportional for AUC0-∞ and C_{max} after single administration and for $C_{max,ss}$ at steady state in the range 2 to12 mg given twice daily for five days. There is no accumulation at multiple-dose conditions.

- Special populations

The PK parameters are similar in healthy volunteers and IBS patients.

To assess the effect of demographic variables on the PK of Zelnorm, exploratory model building was applied to pooled single oral dose data (n=134) from several studies in healthy subjects. Based on exploratory model building, body weight was considered the most important covariate in the analyses, since systemic concentrations of tegaserod were significantly lower in patients with higher body weight. A pooled statistical analysis predicted that the AUC for a patient weighing 100 kg would be 50% lower than for a patient weighing 50kg. A smaller analysis in patients did not confirm the relationship. There appears to be no relationship between weight and response. Given the variability in tegaserod PK, as well as the shallow dose-response relationship, dose adjustment based on individual body weight is not considered to be necessary. Allowing for body weight as the first covariate, no other demographic covariates such as gender, age and ethnic origin, were shown to be of significant influence on any PK parameter of tegaserod in healthy subjects.

An additional special age/gender PK study in healthy volunteers showed a difference in PK parameters between elderly and young females, with higher exposure of tegaserod in elderly females (AUC and C_{max} are 40 and 22% higher, respectively). This finding remains within the variability in Zelnorm PK in healthy subjects, and, is therefore not expected to have clinical relevance. There was no difference between elderly and young males.

The study performed in patients with mild to moderate hepatic impairment showed a significantly increased bioavailability of tegaserod (AUC0-∝ increased by 52 %, AUC_{0-t} by 46% and C_{max} by 26 %). These findings reveal a clear trend towards increased exposure of Zelnorm in patients with impaired hepatic function. Caution would be recommended in patients with mild hepatic impairment. Zelnorm is not recommended to patients with moderate or severe hepatic impairment.

A study performed in patients with severe renal impairment showed that the PK parameters of tegaserod did not change significantly, with the exception of a prolonged mean elimination half-life from 8.5h to 14.1h, which could lead to accumulation of tegaserod in a multiple dose regimen. The tegaserod half-life of 14.1 h would give rise to only a small accumulation at steady state (ca. 25%) and is considered to be of little concern. In addition, systemic exposure (AUC) and peak concentration of the metabolite M29.0 increased 11- and 2.5-fold respectively, in subjects with severe renal impairment compared with healthy controls. However, there are no indications of pharmacological activity of this glucuronide. No dose adjustment would be recommended in patients with mild to moderate renal impairment, but the use of Zelnorm would not be recommended in patients with severe renal impairment.

- Pharmacokinetic interactions

Tegaserod appears to be transported by P-glycoprotein. The P-gp inhibitor quinidine was observed to increase the systemic exposure of tegaserod by 74%. In addition, the distribution to CNS and other "P-gp-protected" tissues may be increased. Other P-gp inhibitors are also likely to affect tegaserod exposure and distribution. Inducers of P-gp may reduce the bioavailability of Zelnorm.

Coadministration of Zelnorm with digoxin resulted in a decreased bioavailability of digoxin (AUC0-∝ decrease by 14 % and C_{max} decrease by 16 %). The predicted concentrations in steady state of digoxin concomitantly administered with tegaserod was 85% of that after administration of digoxin alone, and therefore, plasma concentration monitoring would be recommended when Zelnorm is administered concomitantly.

In one study omeprazole (+bicarbonate) reduced the bioavailability of concomitantly administered tegaserod, possibly as a result of an increased gastric pH. This effect was not observed in another study when tegaserod was administered simultaneously with enteric-coated omeprazol. The effect of an increased pH probably lacks clinical relevance and is not considered to be clinically relevant..

In vivo drug-drug interaction studies with theophylline (CYP1A2 prototype substrate), dextromethorphan (CYP2D6 prototype substrate), warfarin, and oral contraceptives indicate no clinically relevant effects of tegaserod on these drugs and on CYP1A2 or CYP2D6 substrates. *In vitro* studies indicate that tegaserod does not inhibit CYP2C8, 2C9, 2C19, 3A4 and 2E1 *in vivo*.

There were some indications of a modest induction both in tegaserod multiple dose pharmacokinetics and in the interaction studies with digoxin, warfarin and oral contraceptives. Although the effect was small, there may be drug combinations for which this is clinically significant. Therefore tegaserod was examined for its potential to induce CYP3A4 and ABCB1 (P-gp) mRNA, and CYP3A activity in primary human hepatocytes of three individual donors after 72 h of incubation. A slight 3A4 induction was observed in cells from one out of three livers. Both increases in mRNA and 3A4 activity were observed. However, the increases were small and seemed not to be dose-related. The cause of the difference between livers is unknown but large inter-individual variability in inducibility both *in vivo* and *in vitro* has been observed for other inducers. An *in vivo* CYP3A4 induction study with an oral CYP3A4 marker to confirm the complete absence of enzyme induction was not considered to be necessary.

Pharmacodynamics

- Mechanism of action

The pharmacodynamic properties of tegaserod have been evaluated with respect to effects on colonic transit time, colonic tone and phasic motility, small bowel transit time, lower oesophageal sphincter pressure and oesophageal pH, gastric emptying, rectal sensitivity, and anorectal motor activity.

The mechanism of action is shown to be stimulation of the peristaltic reflex (promotile effect on the GIT) via activation of 5-HT_4 receptors in the GIT.

- Primary and Secondary pharmacology

Constipation-IBS (IBS-C)

Study B304 assessed the effect of Zelnorm (2 mg bid during 4 weeks) on rectal sensitivity compared to placebo in 12 patients with IBS-C and rectal hypersensitivity. Zelnorm showed neither a clinically relevant nor a statistically significant difference to placebo in the relative pressure change (relative change from pre-treatment in the lowest distension pressure eliciting rectal pain grade ≥ 4 or the highest pressure reached if no score exceeded 3), rectal compliance during distension, time to first sensation during distension, bloating, urge for defecation, unpleasantness and rectal tone pre- and post-dilatation. In conclusion, Zelnorm at 2 mg bid did not have any significant effect on rectal compliance.

Study B357 assessed the effects of Zelnorm (2 mg bid during 12 days) on GI transit compared to placebo in 24 patients with IBS-C. Zelnorm did not show a statistically significant difference to placebo in both primary efficacy variables: mean colonic transit time was similar in both groups and half proximal colonic emptying time was accelerated by approximately 20% with tegaserod.

Non-clinical findings indicating a decrease in prolactin secretion following administration of tegaserod in rats, led to a study for the determination of prolactin in human plasma. Compared to placebo, single and multiple oral administrations of 25 mg and 100 mg of tegaserod (b.i.d. for 15 days) did not affect prolactin secretion to a clinically relevant extent.

Clinical efficacy

- Dose response studies

A total of three studies B251, B301 and B351 included dose-finding elements. Zelnorm was administered *bid* and within 30 minutes prior to meals. Dosing interval and timing of doses were based on the following considerations:

- IBS symptoms are typically related to meals, and once daily dosing was thought to be unlikely to offer adequate relief from symptoms around both morning and evening meals.
- The pharmacokinetics of tegaserod, with a $t_{1/2}$ of approximately 11 hours and a t_{max} of approximately 1 hour are more consistent with bid dosing than with once daily (o.d) dosing.

In study B251 investigating doses between 0.5 mg bid and 12 mg bid, an apparently bell-shaped dose-response curve was identified in terms of symptom relief. In studies B301 and B351, 6 mg bid was found to be numerically better than 2 mg bid after 4 weeks of therapy. However, data to support the selection of the 6 mg bid dose were considered rather weak.

- Main study

Study A2306

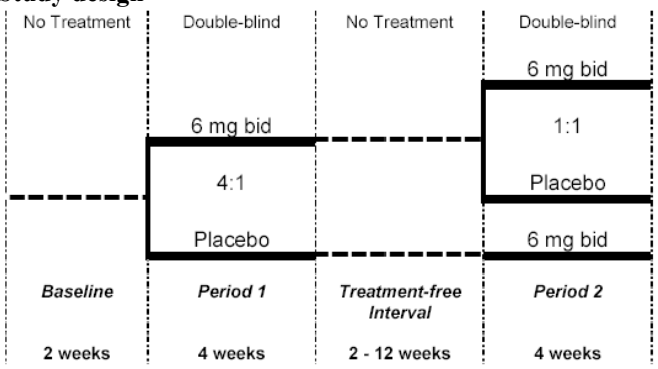
The efficacy claims are based on 1 key study - A2306, with two primary efficacy variables and a 4-week repeated treatment design. Study A2306 was a randomized, double-blind, placebo-controlled, parallel group, multicentre study to assess the efficacy and safety of repeated treatment with tegaserod 6 mg bid and placebo in women with IBS-C.

The study was conducted in 24 countries worldwide.

METHODS

Study A2306 consisted of a 4-week screening period, a 2-week baseline period (no medication), and two 4-week placebo-controlled treatment periods (first and repeated treatment – Period 1 and Period 2), which were separated by a treatment-free interval of 2 to 12 weeks.

Study design



Patients assessed several symptoms either daily or weekly during all study periods. However the decision for inclusion of a patient into Period 2 was based on the weekly assessments of the two primary variables: satisfactory relief of overall IBS symptoms and satisfactory relief of abdominal discomfort/pain.

At the end of Period 1, patients who had at least a partial response (partial responders) entered the treatment-free interval. A partial responder to treatment was defined as a patient who had experienced satisfactory relief of at least one of the primary variables, for at least 2 weeks out of the 4-week treatment period.

In the treatment free interval, patients who experienced a recurrence of symptoms, defined as lack of satisfactory relief of both primary variables in 3 out of 4 consecutive weeks, were eligible to receive repeated treatment.

Non-responders at the end of Period 1 were excluded from further participation in the study.

Study Participants

The study population comprised of women from 18 to 65 years of age, who met ROME II criteria for IBS-C.

Patients had to have at least 12 weeks (not necessarily consecutive) in the preceding 12 months of abdominal discomfort/pain with 2 out of 3 features:

1) relieved with defecation and/or
2) onset associated with a change in frequency of stools and/or
3) onset associated with a change in form (appearance) of stool.

Patients also had to meet the criteria stated in the IBS Questionnaire during the last 3 months prior to study entry.

Patients were excluded if they had 'diarrhoea ≥25%' (significant diarrhoea associated with IBS-C at least 25% of the time during the past 3 months), showed evidence of cathartic colon or a history of laxative abuse, or if they had other significant bowel disorders.

Treatments

In both periods, the study had two treatment arms: placebo or Zelnorm 6 mg. Each patient was required to take one tablet containing tegaserod 6 mg or placebo as appropriate twice daily within 30 minutes before breakfast and the evening meal. Dose variation was not permitted.

The total study duration for an individual patient was between 6 and 26 weeks, depending on the time to recurrence of IBS symptoms.

Objectives
The primary objective of the study was to assess the:
1) 4-week efficacy of Zelnorm during Period 1 and
2) efficacy of re-treatment with Zelnorm during Period 2 in patients who had at least a partial response during Period 1.

The secondary objectives were to assess the:
1) efficacy of Zelnorm on individual IBS symptoms
2) time of onset of IBS symptom relief following tegaserod treatment, using these measures
3) recurrence of IBS symptoms after withdrawal of Zelnorm treatment
4) safety and tolerability of Zelnorm during repeated 4-week treatments.

The tertiary objectives were to assess the:
1) disease specific quality of life (IBS-QoL),
2) health state,
3) work productivity
4) satisfaction with treatment.

Outcomes/endpoints
Two primary endpoints were selected:
1) relief of overall IBS symptoms and
2) relief of abdominal discomfort/pain.

These primary endpoints were assessed on a weekly basis, using a binary scale (yes/no) with the following questions:

- Did you have satisfactory relief of your overall IBS symptoms during the last week?
- Did you have satisfactory relief of your abdominal discomfort or pain during the last week?

During each treatment period, a responder for satisfactory relief of overall IBS symptoms and satisfactory relief of abdominal discomfort/pain was defined as a patient who recorded satisfactory relief, for at least 3 out of the first 4 weeks of that period ("75% rule").

Primary efficacy variables were analyzed for each treatment period:
1. Response for satisfactory relief of overall IBS symptoms during first treatment
2. Response for satisfactory relief of overall IBS symptoms during repeated treatment
3. Response for satisfactory relief of abdominal discomfort/pain during first treatment
4. Response for satisfactory relief of abdominal discomfort/pain during repeated treatment

To examine if the response of the primary variables was consistent with individual symptom response, the association between the primary variables and individual symptoms was evaluated.

Secondary efficacy variables included:

- Relief of overall IBS symptoms and abdominal discomfort/pain using a second responder definition, requiring at least 2 weeks with satisfactory relief within the first 4 weeks of treatment (50% rule).
- Daily assessments of individual IBS symptoms, namely: intensity of abdominal discomfort/pain and abdominal bloating, stool consistency and stool frequency.
- Weekly assessment of relief of constipation
- The time to onset of improvement of overall and individual IBS symptoms based on daily and weekly assessments mentioned above.

Tertiary efficacy variables were assessed using questionnaires for the quality of life (IBS-QoL), satisfaction with treatment, health state evaluation (EQ-5D), and Work Productivity and Activities Impairment for IBS (WPAI-IBS).

Sample size
The samples were calculated in order to detect a treatment difference of 15% in relief of overall IBS symptoms and 10% in relief of abdominal discomfort/pain during each treatment period, at an assumed placebo response rate of 50%.

A sample size of 2000 patients in the Zelnorm group and 500 patients in the placebo group in Period 1, and 535 per treatment group in Period 2 was considered sufficient based on the above listed criteria with 85% power at a significance level of 0.05.

The target enrolment for Period 1 was 2500 women with IBS-C, randomised in a 4:1 ratio (Zelnorm: 2000, placebo: 500) using an IVR (Interactive Voice Randomisation) System. For Period 2, the enrolment target was 1070 patients randomised in a 1:1 ratio, who were on Zelnorm during Period 1 and showed at least a partial response, and whose symptoms recurred during the treatment-free interval.

Randomisation
During Period 1, patients were randomly assigned to either Zelnorm or placebo (allocation ratio 4:1). In Period 2 those who were in the tegaserod group in Period 1 were randomized to either Zelnorm or placebo (allocation ratio 1:1). Those who were in the placebo group during Period 1 were assigned (mock randomised) to tegaserod in Period 2.

Blinding (masking)
The double-blind study drugs (tegaserod and placebo) were identical with regard to color, appearance, and packaging. Emergency code breaks for serious adverse events were performed using the IVR System.

Statistical methods
The intent-to-treat (ITT) population of Period 1 was defined as all patients randomized into Period 1, irrespective of whether or not they took any study medication.

The ITT population in the treatment free interval was defined as all patients in the ITT population in Period 1 who entered the treatment free interval.

The ITT population of Period 2 was defined as all patients from the Zelnorm group in Period 1 that were randomized to study treatment in Period 2. The ITT placebo-Zelnorm population in Period 2 was defined as all patients who received placebo during Period 1 and were (mock) randomized to tegaserod in Period 2.

Using the ITT populations, relief of overall IBS symptoms and of abdominal discomfort/pain during the first and repeated treatment were compared between treatment periods using the Cochran-Mantel-Haenszel test, stratified by centre. Treatment differences and 95% confidence intervals presented were calculated using this model.

The analysis of the 2 primary efficacy variables, at 2 timepoints used a sequentially rejective multiple testing procedure on the four statistical tests in order to maintain the overall two-sided significance level of 0.05. The testing hierarchy followed the order as presented in the list of the primary efficacy variables mentioned above.

The Per Protocol (PP) population was generally defined as all ITT patients without any major protocol violations.

Odds ratios were calculated based on logistic regression models.

Longitudinal analyses of the weekly response rates were performed using General Estimation Equation (GEE) models, with p-values derived for each week and overall week 1-4.

In addition, Number Needed to Treat (NNT), calculated as the reciprocal of the treatment difference in responder rates is presented.

Secondary and tertiary efficacy variables were analysed with appropriate statistical methods. No corrections for multiple testing were applied.

Background information, demographics, study medication, concomitant medications, study completion information, and safety data were listed and summarized descriptively by treatment group.

RESULTS

Participant flow
A total of 4689 patients from 24 countries were screened. The most frequent reason for screen failure before baseline was withdrawal of consent. Most patients who entered baseline and were not randomized did not meet the diagnostic/severity criteria. Few patients were discontinued during first treatment. Reasons for discontinuation were similar for both groups, the most common reason being unsatisfactory therapeutic effect. Very few patients were discontinued during repeated treatment with similar reasons in both treatment groups. The percentage of patients that withdrew due to adverse events was similar for both placebo and Zelnorm in all the periods of the study.

There were 3 randomized patients who were 66 years of age. These patients are included throughout the analyses presented (even though headers indicate “women, up to 65 years”). Protocol deviations did not affect the study results.

Conduct of the study
The study was performed according to Good Clinical Practice recommendations and following all international ethics principles, according to the applicant.

Baseline data
Demographic and baseline characteristics were similar across treatment groups. Most patients were Caucasian, pre-menopausal and between the ages of 25 and 55 years, with an overall mean age of 42.0 years. Nearly all patients fulfilled the Rome I and Rome II criteria. A high grading of discomfort and bloating was noticed compared with prior studies.

Table 2 – Disease duration and severity

	Study A2306	
	6 mg bid tegaserod N = 2135	placebo N = 525
Disease duration		
Mean (years, SD)	13.1 (11.4)	13.4 (12.0)
Median (years)	10.0	10.0
< 5 years, n (%)	566 (26.5)	130 (24.8)
5 - 10 years, n (%)	639 (29.9)	160 (30.5)
Disease severity – mean number/week (SD)		
Bowel movements	3.6 (2.86)	3.8 (3.53)
Disease severity – mean % of the highest possible score		
Hardness of stool[1]	72%	72%
Abd. discomfort/pain[2]	78%	78%
Abd. bloating[2]	82%	82%

[1] Best rating is 50%
[2] Best rating is 0%

Numbers analysed
The number of patients analysed in different analysis populations for Period 1 and Period 2 is shown in the Tables below.

Table 3 - Analysis populations for Period 1 (ITT patients in P1)

Analysis population	Tegaserod 6 mg bid N=2135 n (%)	Placebo N=525 n (%)	Total N=2660 n (%)
Intent-to-treat in P1	2135 (100)	525 (100)	2660 (100)
Safety analyzable in P1	2132 (99.9)	525 (100)	2657 (99.9)
Per Protocol in P1	1899 (88.9)	460 (87.6)	2359 (88.7)
Health economic in P1	770 (36.1)	179 (34.1)	949 (35.7)

Source: PTT 7.3-1

Table 4 - Analysis populations for Period 2 (ITT patients in P2)

Analysis population	Teg 6 mg bid - Teg 6 mg bid N=488 n (%)	Teg 6 mg bid - Placebo N=495 n (%)	Placebo - Teg 6 mg bid N=208 n (%)	Total N=1191 n (%)
Intent-to-treat in P2	488 (100)	495 (100)	208 (100)	1191 (100)
Safety analyzable in P2	487 (99.8)	494 (99.8)	208 (100)	1189 (99.8)
Per Protocol in P2	378 (77.5)	365 (73.7)	150 (72.1)	893 (75.0)
Health economic in P2	256 (52.5)	254 (51.3)	114 (54.8)	624 (52.4)

Source: PTT 7.3-3

In Period 1, 301 patients were excluded from the PP population. The most common reasons for exclusion were:

- Use of laxatives > 1 day/week (172 patients).
- Mean stool consistency score < 4 during the last 14 days of baseline (52 patients).
- Satisfactory relief for either of the primary efficacy variables during either of the 2 weeks of

baseline (45 patients).

A total of 298 patients were excluded from the PP population in Period 2. The most common reasons for exclusion were:

- Recurrence criteria in treatment-free-interval not fulfilled (122 patients).
- Partial response criteria in Period 1 not fulfilled (102 patients).
- Use of laxatives > 1 day/week (71 patients).

The primary population for efficacy analysis was the ITT population and therefore only the ITT results are discussed in this report. The PP population was used in supportive analyses. This approach was considered adequate by the CHMP.

Outcomes and estimation

Two response criteria were prospectively defined for relief of symptoms:

- satisfactory relief of IBS symptoms for at least 3 out of 4 weeks (primary efficacy variable, 75% rule) and
- satisfactory relief of IBS symptoms for at least 2 out of 4 weeks (secondary efficacy variable, 50% rule).

Results for relief of overall IBS symptoms and abdominal discomfort or pain for at least 3 out of 4 weeks (primary efficacy variable, 75% rule) are shown in the following table.

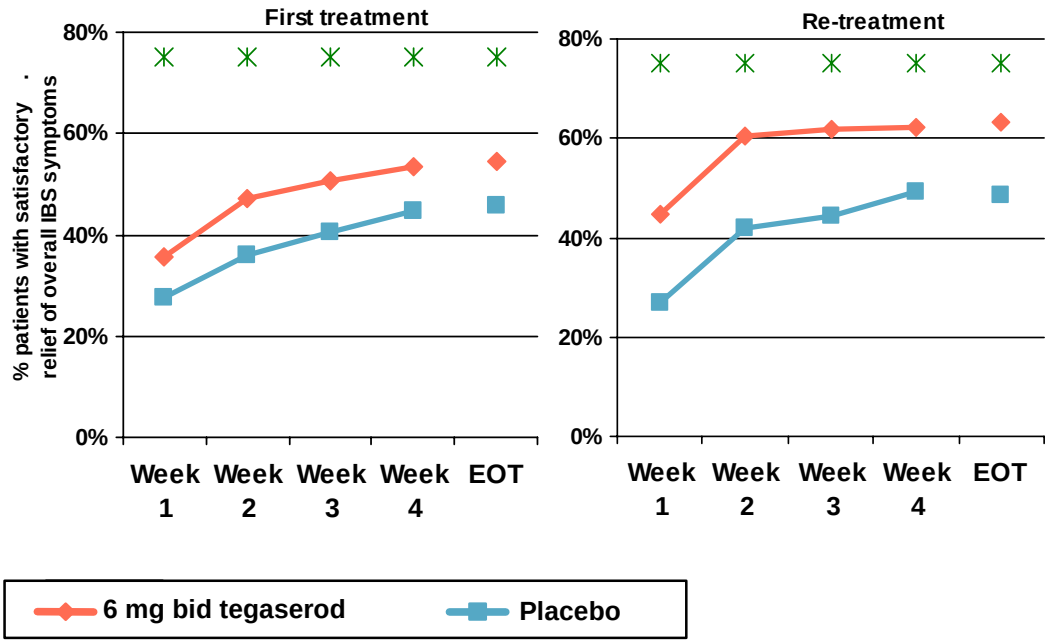
Table 5 - Results in the primary variables in the ITT population for period 1 and period 2 (re-treatment)

	Period 1		Period 2	
	Tegaserod n=2135	**Placebo n=525**	**Tegaserod n=488**	**Placebo n=495**
Relief of overall IBS symptoms				
Number of responders (%)	719 (33.7%)	127 (24.2%)	219 (44.9%)	142 (28.7%)
Difference in response rate *	9.3		16.6	
95 % CI for difference	(5.3 , 13.3)		(10.9 , 22.2)	
p-value *	<0.0001		<0.0001	
Odds ratio	1.63		2.13	
95 % CI for odds ratio **	(1.30 , 2.04)		(1.61 , 2.80)	
Relief of abdominal discomfort or pain				
Number of responders (%)	669 (31.3%)	116 (22.1%)	207 (42.4%)	134 (27.1)
Difference in response rate *	9.1		15.9	
95 % CI for difference	(5.2 , 13.0)		(10.3 , 21.5)	
p-value *	<0.0001		<0.0001	
Odds ratio	1.64		2.14	
95 % CI for odds ratio **	(1.30 , 2.07)		(1.62 , 2.84)	

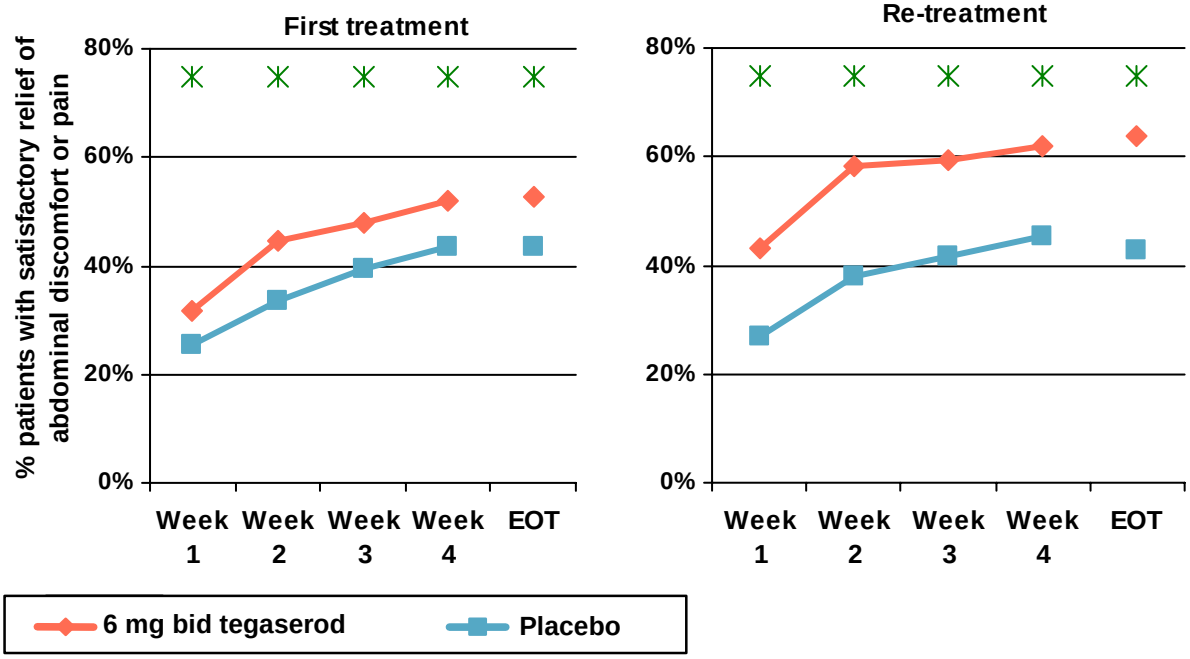
* From the CMH test.

** From the logistic regression including covariates.

Proportion of patients with satisfactory relief of overall IBS symptoms



Proportion of patients with satisfactory relief of abdominal discomfort/pain

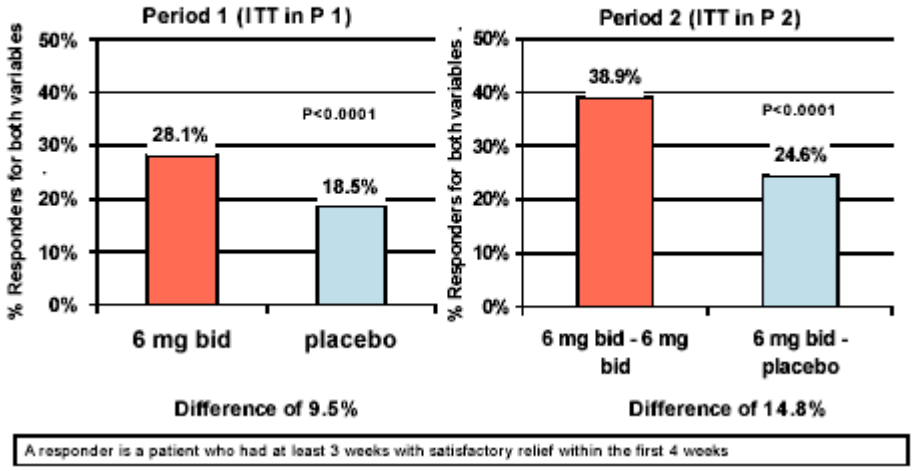


Combined response for overall IBS symptoms and abdominal discomfort or pain

In Period 1, the majority of patients meeting the response definition for one variable (relief of overall IBS symptoms), were also responders for the second variable (relief of abdominal discomfort or pain). Few patients (<5.7%) were responders for only one variable.

The combined response according to the 75% rule (i.e. responders for both relief of overall IBS symptoms and relief of abdominal discomfort or pain) was statistically significantly higher in the Zelnorm (tegaserod) group compared to placebo in both treatment periods (9.5% in Period 1 and 14.8% in Period 2), but failed to reach the pre-defined 15%.

Figure 9-7 **Combined response rates for relief of overall IBS symptoms and relief of abdominal discomfort or pain, during Period 1 and Period 2 (ITT patients)**



Secondary efficacy

Using the 50% rule, 50.5% of patients receiving Zelnorm had satisfactory relief of overall IBS symptoms compared to 39.8% receiving placebo during Period 1. With repeated treatment, 60.5% of patients receiving Zelnorm and 42.8% receiving placebo reported satisfactory relief. Both treatment differences, 10.6% and 17.0%, were significant ($p<0.0001$). For first and repeated treatment, the NNT were 9.4 and 5.9, and the odds ratios were 1.58 and 2.16.

Applying the 50% rule, with first treatment, 47.8% of patients receiving Zelnorm had satisfactory relief of abdominal discomfort/pain compared to 38.7% receiving placebo. With repeated treatment, 58.8% of patients receiving Zelnorm and 38.8% receiving placebo reported satisfactory relief. Both treatment differences, 9.0% and 19.9%, were statistically significant ($p<0.0003$). For first and repeated treatment, the NNT were 11.1 and 5.0, and the odds ratios were 1.48 and 2.51.

Maintenance of effect

During the evaluation, further data were presented by the applicant on the proportion of patients having responded during Period 1, who maintain the same or higher level of response during Period 2. In Table 6 the response in Period 2 among patients who responded in Period 1 are presented for relief of overall symptoms of IBS and for relief of discomfort/pain separate and combined for the tegaserod-tegaserod and the tegaserod-placebo groups.

Table 6 - Period 2 response by Period 1 response for overall relief and abdominal/discomfort pain relief (all ITT patients Period 2)

Study A2306	Period 2 Response													
			At least 75%						At least 50%					
	All patients Total (=100%)		Overall relief		Disc/pain relief		Overall & disc/pain relief		Overall relief		Disc/pain relief		Overall & disc/pain relief	
	Teg	Plac	Teg	Plac	Teg	Plac	Teg	Plac	Teg	Plac	Teg	Plac	Teg	Plac
Period 1 Response	N	N	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Overall relief														
• At least 75% response	288	298	51.4	34.2	-	-	46.5	28.5	66.3	48.7	-	-	61.1	40.9
• At least 50% response	423	422	46.8	30.1	-	-	41.1	25.8	63.6	44.3	-	-	58.4	38.2
Discomfort/pain relief														
• At least 75% response	262	276	-	-	50.4	30.8	47.3	29.0	-	-	66.4	44.2	62.2	41.7
• At least 50% response	395	403	-	-	45.8	29.5	42.0	27.0	-	-	63.8	41.4	59.2	39.5
Overall and disc/pain relief														
• At least 75% response	237	248	54.9	35.9	52.7	31.9	49.8	30.2	68.4	49.2	67.5	45.2	64.1	42.7
• At least 50% response	372	375	47.6	31.5	46.2	29.9	42.7	27.5	64.8	46.1	64.0	41.9	60.5	40.0

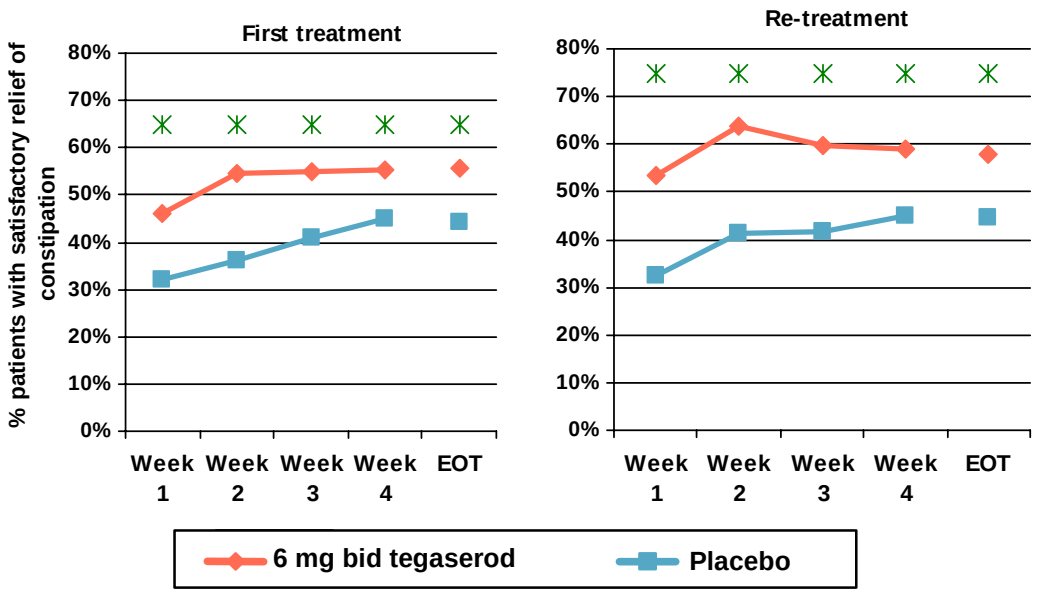
Recurrence

During the treatment-free interval approximately 50% of the ITT responders experienced a recurrence of symptoms within 4 weeks and 70% within 8 weeks. There were more tegaserod-treated patients with recurrence at each week compared to placebo treated patients. Similarly, the proportion of patients requiring an increased laxative intake, and the number of days on laxatives, tended to be higher among those being treated with Zelnorm during the first period.

Weekly relief of constipation

The proportion of patients reporting satisfactory relief of constipation was statistically significantly greater with Zelnorm than with placebo during first and second treatment periods, as shown in the next figure.

Proportion of patients with satisfactory relief of constipation



✳ p<0.05, Tegaserod versus placebo, using GEE analysis for Wks 1-4 and logistic regression for EOT.
EOT = end of treatment, Only values during the last 7 days of treatment are considered for EOT.

Statistical significance favouring Zelnorm (tegaserod) was achieved for the remaining secondary endpoints including stool frequency and consistency, weekly number of days with no bowel movements, early effect (Days 1-7) on bowel movements and stool consistency; number of days with hard or very hard stools and the other assessments of abdominal discomfort or pain, bloating, bowel movements.

Tertiary efficacy

➢ IBS-QoL (Quality of Life)

Tegaserod-treatment showed a statistically significant effect on the IBS-QoL versus placebo on the overall score, as well as on 5 of the 8 domains (dysphoria, body image, health worry, food avoidance, and relationship).

➢ Overall satisfaction with treatment

There was a statistically significantly greater proportion of patients in the Zelnorm group who reported:

- satisfactory relief of abdominal pain/discomfort, constipation, and other symptoms,
- level of expectations being met or exceeded,
- greater relief of IBS symptoms with study medication versus previous medication use,
- willingness to use the drug in the future,
- willingness to recommend the medication to other patients with IBS

➢ EQ-5D health state questionnaire

The EQ-5D health state questionnaire was introduced after the start of the study, in protocol amendment 1. The questionnaire was completed at baseline and end of first treatment by 238 Zelnorm patients and 44 placebo patients. Considering the small numbers of patients, trends seen in the EQ-5D results did not reach statistical significance.

➢ Work productivity and activity impairment (WPAI-IBS)

Baseline values in WPAI-IBS scores were balanced between treatment groups and indicative of a population with working and activity impairment. Patients on Zelnorm had significantly greater work productivity compared with placebo patients such as; greater presenteeism (5.4% improvement over

placebo), less absenteeism (2.6% improvement over placebo), less work impairment (6.3% improvement over placebo), less activity impairment (3.5% improvement over placebo).

Table 7 - Summary of the results of the primary, secondary and tertiary efficacy variables

Type of variable	Variable	First treatment			Re- treatment		
		Teg (n=2,135)	Placebo (n=525)	P value	Teg (n=488)	Placebo (n=495)	P value
Primary	Relief of overall symptoms	33.7%	24.2%	<0.0001	44.9%	28.7%	<0.0001
	Relief of abdominal discomfort/pain	31.3%	22.1%	<0.0001	42.4%	27.1%	<0.0001
Secondary	Relief of overall symptoms (50% rule)	50.5%	39.8%	<0.0001	60.5%	42.8%	<0.0001
	Relief of abdominal discomfort/pain (50% rule)	47.8%	38.7%	0.0002	58.8%	38.8%	<0.0001
	Improvement† in abdominal discomfort/pain	52.5%	42.8%	<0.0001	54.2%	41.8%	<0.0001
	Improvement† in bloating	50.6%	40.1%	<0.0001	54.4%	41.2%	<0.0001
	Relief of constipation (75% rule)	39.4%	24.8%	<0.0001	45.1%	27.5%	<0.0001
	Mean stool consistency, change from baseline	–1.1	–0.7	<0.0001	–0.9	–0.6	0.0003
	Weekly bowel movements, change from baseline	2.5	1.3	<0.0001	2.2	1.5	0.0013
Tertiary	**Satisfaction with study medication for IBS symptoms**	**35.6%**	**25.1%**	<0.0001	50.3%	34.3%	<0.0001
	Study medication relief; expectations for IBS symptoms	**27.4%**	**18.3%**	<0.0001	35.6%	26.6%	<0.0001
	Better relief of study medication vs previous medication	**55.7%**	**43.0%**	<0.0001	71.6%	55.2%	<0.0001

Teg = Zelnorm (tegaserod)

- Ancillary analyses

No ancillary analysis have been performed

- Clinical studies in special populations

No studies assessing efficacy in special populations have been performed.

- Supportive studies

Five placebo-controlled supportive studies were submitted (see Table 1).

- Analysis performed across trials (pooled analyses and meta-analysis)

The applicant provided additional information to support the efficacy, based on the results of the 5 supportive, double blind 3-month studies that were reanalysed focusing on the first 4 weeks of therapy, in women below 65 years of age and, as far as possible, on response rates based on similar, but less stringent outcome measures as those in the pivotal study. A meta-analysis of previous clinical trials was performed to claim consistency of the results with the pivotal study A2306 (See below and Discussion on clinical efficacy).

Table 8 - Responder rates for overall relief during first 4 weeks of treatment from 6 major studies (3 using 75% rule for binary efficacy scale[1] plus 3 using 50/100% rule for ordinal efficacy scale[2]) in IBS Phase III (women ≤ 65 years)

Study	Tegaserod 6 mg bid	Placebo	Odds Ratio[3]	Difference	p-Value[5]
A2306[1]	719/2135 (33.7 %)	127/525 (24.2%)	1.63 [1.30—2.04]	9.3% [5.3—13.3]	< 0.0001
AFI01[1]	51/285 (17.9%)	35/268 (13.1%)	1.45 [0.91—2.31]	5.0% [-1.0—11.0]	0.1052
ASG01[1]	105/226 (46.5%	57/232 (24.6%)	2.66 [1.79—3.96]	22.0% [14.0—30.1]	< 0.0001
B301[2]	81/220 (36.8%)	44/223 (19.7%)	2.37 [1.54—3.64]	17.7% [10.8—24.6]	< 0.0001
B351[2]	95/223 (42.6%)	62/221 (28.1%)	1.90 [1.28—2.83]	14.8% [6.7—22.9]	0.0013
0358[2]	302/749 (40.3%)	189/731 (25.9%)	1.94 [1.55—2.42]	14.2% [9.9—18.6]	< 0.0001
Meta-analyzed [4]	--	--	1.87 [1.64—2.11]	12.1% [9.6—14.5]	< 0.0001

1: Responder at least 3 positive evaluations during the first 4 weeks of treatment (binary scale, 75% rule)

2: Responder completely or considerably relieved in 50% of weeks, or at least somewhat relieved during all 4 weeks (ordinal scale, 50/100% rule)

3: OR from logistic regression

4: Hedges & Olkin (1985) Statistical Methods for Meta-Analysis, Orlando: Academic Press

5: CMH Test (Study * Tmt interaction n.s., p=0.1811)

- Discussion on clinical efficacy

The magnitude of the treatment effect in the pivotal study did not meet the pre-specified objectives. Instead of a 15% (absolute) difference in response rate, which in the view of the CHMP was considered a treatment difference necessary to allow conclusion of clinical relevance, only a 9+% difference was achieved in the first treatment period – Period 1. The combined response rates for Period 1, i.e. relief of overall symptoms and pain were 28.1% vs. 18.5% [95% CI; 6%; 14%]. Secondary endpoints, including effects on constipation, pain relief, bloating, stool consistency, bowel movements, were statistically significant but the magnitude of the treatment effects in absolute terms was as low as those reported for the co-primary endpoints.

In most patient-derived outcome measures, the absolute difference between placebo and Zelnorm (tegaserod) was between 10 to 15%. This was true also in cases where a large placebo/study effect is present, such as "Would you use the study medication in the future for IBS?" - 77% (Zelnorm) vs. 64% (placebo).

It was noted that the placebo effect was between 22-29%, rather than the assumed 50%. Although the onset of relief with Zelnorm appears to be rapid, it is nevertheless noted that the response pattern to both placebo and Zelnorm run in parallel over the evaluation period, indicating that the response to placebo increases over time.

The applicant provided further arguments to support the clinical relevance of the findings, which are summarised below together with CHMP's view on these:

- For individuals identified as responders to treatment, there was on average an improvement in the key symptoms from baseline, i.e. abdominal discomfort/pain, bloating, and stool consistency corresponding to 1.4 to 2.1 points on the 7-point scale. This magnitude of improvement was also seen for patients identified as responders by the co-primary variable, satisfactory relief of

abdominal pain in study A2306. The applicant argues that a change of 0.5 points or more on the 7-point scale is generally considered clinically meaningful. The CHMP, however, has not questioned the relevance of "response" according to agreed criteria, but the low percentage of responders. In this context it may be noted that the change in placebo responders was approximately similar for all key symptoms except for number of bowel movements/week where the difference, in line with the mechanisms of action, differed in favour of Zelnorm (tegaserod).

- To allow a comparison with the A2306 results, earlier studies were retrospectively analyzed for the treatment effect after 4 weeks in the target population, using the 75% rule, where possible. Disease characteristics at baseline were similar between the studies. Responder rates for overall symptom relief were consistent across studies and variables in the key study A2306 and the 5 supportive trials.

  Based on a fixed effects meta-analytic algorithm (Cochrane Collaboration manual) the mean therapeutic gain across all studies was 12.1% [CI 9.6; 14.3], corresponding to a NNT of 8.3 [CI 6.9; 10.4]. If the meta-analysis is applied on the study results based on the "50% rule" response definition, the mean treatment gain is 13.8% [CI 11.2; 16.3] and the NNT 7.3 [CI 6.1; 9.0]. The CHMP noted these results, as well as the fact that a treatment gain of 15% in the relief of overall IBS symptoms could not be demonstrated. Importantly, while these studies provide conceptual support, more weight must be put on the effect size estimate derived from the pivotal study.

Despite the arguments put forward by the applicant relating to consistency between studies and different patient derived outcome measures such as QoL, presentism at work, etc, the modest activity observed with Zelnorm (tegaserod) was seen as a major concern.

Maintenance of the treatment effect

The selection criteria for Period 2 led to an enrichment of the patient population, where 46% of the patients entered the second cycle. In an enriched population, a high response rate is expected. In this respect, the increase in the response rate in Period 2 (approximately 45% Zelnorm vs. 29% placebo; i.e. 16% absolute difference) in the relief of overall IBS symptoms as compared to Period 1 (approximately 34% Zelnorm vs. 24% placebo) was modest, and not considered to be convincing. This suggests a significant inter-occasion variability, but a possible loss of a substantial part of the treatment effect with subsequent treatment courses is a concern. The fact that not only patients with complete response, but also patients with partial response were eligible for the second period is likely to have influenced the response rate observed in Period 2. It was therefore not considered possible to make an accurate assessment of the magnitude of the treatment effect that is lost in subsequent treatment courses.

In this context it should be noted that 2 out of 3 patients treated with placebo found that the results of therapy were sufficiently good to support the use of "placebo" in patients with IBS-C (vs. 3 out of 4 on Zelnorm). These results cannot be translated to what would happen in clinical practice where, on the one hand, the study effect is absent and, on the other hand, patients know that they are on active therapy. Several single arm studies indicate that between 2/3 to 5/6 of patients report "satisfactory relief" of IBS symptoms.

The applicant provided further information in response to this issue. The response in Period 2 of the patients by response in Period 1 were presented for relief of overall symptoms of IBS and for relief of discomfort/pain separate and combined for the tegaserod-tegaserod and the tegaserod-placebo groups. In the tegaserod-group for both variables the responder rates in Period 2 was about 50% using the 75% rule, and the responder rate using the 50%-rule in Period 2 was about 64%. Responder rates for the combined endpoint were between 50% and 61%, respectively. Although the difference from placebo in Period 1 in this population has not been assessed, the incremental effect over placebo in Period 2 ranged between 12 - 20% (75% rule) and 20 – 22% (50% rule) for the individual and the combined variables.

In view of the data and the arguments provided by the applicant, the CHMP was not assured of the maintenance effect of Zelnorm (tegaserod) in recurrent IBS-C.

Recurrence

During the treatment-free interval approximately 50% of the ITT responders experienced a recurrence of symptoms within 4 weeks and 70% within 8 weeks. There were more Zelnorm-treated patients with recurrence at each week compared to placebo treated patients. Similarly the proportion of patients requiring an increased laxative intake, and the number of days on laxatives, tended to be higher among those being treated with Zelnorm during the first period.

The applicant argued that this may reflect the patient's desire to compensate for the withdrawal of a pharmacological active compound and that the provided data support the absence of a rebound phenomenon. However the CHMP disagreed, considering the data from Study 0358, which show similar results even if non-responders were not excluded. The observed trend in the use of laxatives and the small differences in the rate of reappearance of IBS symptoms during the treatment free interval were recognised, and the possibility of a rebound phenomena was considered to be a matter of concern.

On 16 November '05, the CHMP invited gastroenterology experts to the CHMP discussion on Zelnorm and to the oral explanation made by the applicant. During this oral explanation, the applicant presented the available data to argue the clinical relevance of the efficacy and a favourable safety profile of Zelnorm (tegaserod). Following this discussion, some experts supported the view that the small effect size was not considered to be clinically relevant.

The magnitude of the treatment effect that did not meet the pre-specified objectives and the clinical relevance of the observed efficacy was seriously questioned by the CHMP. Moreover, in the second period, which studied an enriched population, the effect size was smaller than expected from the results in Period 1. Hence, available data do not support maintenance of an effect.

Clinical safety

- *Patient exposure*

Tegaserod (the active substance of Zelnorm) is currently authorised in 56 countries for the treatment of IBS-C at a dose of 6 mg bid and for a duration of up to 3 months. The estimated number of patient years is about 300,000 (March 31st 2004).

The key 4-week safety population comes from 6 studies with a total of 3032 patients on tegaserod and 2166 patients on placebo, while the largest controlled data set including also other indications encompasses about 9000 patients on tegaserod and 5000 on placebo. Included here are two long-term (52 w.) dose-comparative (2mg vs. 6mg bid) studies in a total of about 1400 patients.

- *Adverse events (AE)*

Table 9 - Adverse events - most frequently affected system organ classes (up to 2% in any group) (key 4 week safety population).

	tegaserod 2 mg bid N=1119 n (%)	tegaserod 6 mg bid N=4286 n (%)	tegaserod all N=5405 n (%)	placebo N=2937 n (%)
Total number (%) of patients with AEs	634 (56.7)	1514 (35.3)	2148 (39.7)	1050 (35.8)
System organ class affected:				
Gastrointestinal disorders	342 (30.6)	673 (15.7)	1015 (18.8)	415 (14.1)
Nervous system disorders	217 (19.4)	383 (8.9)	600 (11.1)	297 (10.1)
Infections and infestations	105 (9.4)	346 (8.1)	451 (8.3)	281 (9.6)
Musculoskeletal & connective tissue disorders	78 (7.0)	167 (3.9)	245 (4.5)	108 (3.7)
General disorders & administrative site conditions	90 (8.0)	141 (3.3)	231 (4.3)	122 (4.2)
Skin & subcutaneous tissue disorders	39 (3.5)	86 (2.0)	125 (2.3)	71 (2.4)
Psychiatric disorders	41 (3.7)	73 (1.7)	114 (2.1)	48 (1.6)
Reproductive system & breast disorders	25 (2.2)	57 (1.3)	82 (1.5)	44 (1.5)
Metabolism & nutrition disorders	22 (2.0)	31 (0.7)	53 (1.0)	23 (0.8)

Table 10 - Adverse events - most frequent events (up to 2% in any group) (key 4 week safety population)

	tegaserod 2 mg bid N=1119 n (%)	tegaserod 6 mg bid N=4286 n (%)	tegaserod all N=5405 n (%)	placebo N=2937 n (%)
Total number (%) of patients with AE(s)	634 (56.7)	1514 (35.3)	2148 (39.7)	1050 (35.8)
Adverse event preferred term:				
Headache	152 (13.6)	298 (7.0)	450 (8.3)	222 (7.6)
Abdominal pain	148 (13.2)	172 (4.0)	320 (5.9)	137 (4.7)
Diarrhoea	82 (7.3)	223 (5.2)	305 (5.6)	53 (1.8)
Nausea	68 (6.1)	141 (3.3)	209 (3.9)	100 (3.4)
Flatulence	64 (5.7)	75 (1.7)	139 (2.6)	69 (2.3)
Dizziness	46 (4.1)	53 (1.2)	99 (1.8)	52 (1.8)
Dyspepsia	42 (3.8)	56 (1.3)	98 (1.8)	38 (1.3)
Nasopharyngitis	27 (2.4)	65 (1.5)	92 (1.7)	44 (1.5)
Back pain	31 (2.8)	57 (1.3)	88 (1.6)	47 (1.6)
Constipation	24 (2.1)	16 (0.4)	40 (0.7)	13 (0.4)

An increased incidence of gastrointestinal adverse reactions, mainly diarrhoea, has been documented. These events relate to the pharmacology of tegaserod. The short time to onset of diarrhoea is noticeable and underscores the pharmacological character of this adverse reaction.

Generally, no action or intervention was necessary in patients reporting diarrhoea. Dose adjustment, interrupting, or discontinuation of treatment or use of concomitant medication(s) related to diarrhoea were more frequent with tegaserod than placebo. In one case (2 mg bid, Day 1) diarrhoea was associated with dizziness and hypotension and led to discontinuation from the study.

Analyses performed for double-blind 4- and 12-week studies within this subset indicate that headache is the most frequent single adverse event, both in the Zelnorm (tegaserod) and the placebo treatment groups.

Table 11 - Patients experiencing diarrhoea (key 4-week safety population)

	Tegaserod 2 mg bid	Tegaserod 6 mg bid	Tegaserod all	Placebo
	N=1119 n (%)	N=4286 n (%)	N=5405 n (%)	N=2937 n (%)
No. of patients with diarrhoea	87 (7.8)	252 (5.9)	339 (6.3)	73 (2.5)
No. without clinical consequences	86 (7.7)	252 (5.9)	338 (6.3)	73 (2.5)
No. with serious consequences	1 (0.1)	0	1 (0.02)	0
0 episodes	1032 (92.2)	4034 (94.1)	5066 (93.7)	2864 (97.5)
1 episode	70 (6.3)	223 (5.2)	293 (5.4)	67 (2.3)
	N=87 mean (SD)	N=252 mean (SD)	N=339 mean (SD)	N=73 mean (SD)
1 day to first onset	34 (39.1)	101 (40.1)	135 (39.8)	4 (5.5)
2 to 7 days to first onset	20 (23.0)	67 (26.6)	87 (25.7)	13 (17.8)
8 to 28 days to first onset	31 (35.6)	78 (31.0)	109 (32.2)	53 (72.6)
No action taken	71 (81.6)	141 (56.0)	212 (62.5)	51 (70.8)
Dosing adjusted / interrupted	1 (1.1)	36 (14.3)	37 (10.9)	10 (13.9)
Study drug discontinued	15 (17.2)	48 (19.0)	63 (18.6)	5 (6.9)
Concomitant medication taken	13 (14.9)	54 (21.4)	67 (19.8)	12 (16.7)
Max. duration of episodes (days)	16.6 (26.1)	12.0 (22.8)	13.2 (23.7)	11.6 (23.0)
Time to first episode (days)	8.2 (9.2)	7.1 (8.5)	7.3 (8.7)	15.6 (8.6)
Duration of first period (days)	15.9 (25.7)	11.6 (22.2)	12.7 (23.2)	11.6 (23.0)
Severity of diarrhoea*	N=82 n (%)	N=223 n (%)	N=305 n (%)	N=53 n (%)
mild severity	20 (1.8)	94 (2.2)	114 (2.1)	20 (0.7)
moderate severity	33 (2.9)	91 (2.1)	124 (2.3)	23 (0.8)
Severe	29 (2.6)	38 (0.9)	67 (1.2)	10 (0.9)

Estimates of the incidence of diarrhoea with clinically significant consequences (CSC-diarrhoea) associated with the long-term (repeated courses) use of tegaserod have been provided. In the controlled studies, rare cases of CSC-diarrhoea were reported in 3/9284 patients (0.03%) on tegaserod, and in uncontrolled studies 1/5877 patients (0.02%) on tegaserod. The time between onset of tegaserod therapy and the occurrence of CSC-diarrhoea in the 4 reported cases was 1-49 days (median 4.5 days)

Based on the worldwide sales data up to 30 April 2005, there are 43 cases of CSC-diarrhoea resulting in a reporting rate of 43/640,215 patient-years, or 6.7 cases/100,000 patient-years. The duration of tegaserod treatment prior to the occurrence of the CSC-diarrhoea in the post-marketing experience was between 1 and 7 days in the 21 patients for whom exposure data were available.

- Serious adverse event/deaths/other significant events

There were 6 deaths in clinical development, 1 in the key 4 week safety population and 5 in other populations (5 IBS patients and 1 chronic constipation patient); 3 during the study or in the 30-day follow-up period, and 3 at a later stage. Patients who died had all taken tegaserod, but no deaths were felt by the investigator to be related to study drug, demographic factors or other therapies.

Table 12 - Deaths in clinical studies (all indications, all trials)

Age, Gender, Race Treatment duration	Main event	Comment
Tegaserod 2 mg bid		
57, woman, Caucasian, on study drug for 36 days	Suicide	long history of depression, treated with amitriptyline, died during treatment.
85, man, Caucasian, on study drug for 84 days	Respiratory failure	history prior to study, diagnosis of mesothelioma & asbestosis, died 67 days after last dose.
Tegaserod 6 mg bid		
88, woman, Caucasian, on study drug for 118 days	Cholestasis, pulmonary embolism	Hospitalised for suspected ductal carcinoma in situ or pancreatic cancer, died 119 days after last dose.
68, woman, Caucasian, on study drug for 30 days	Suicide	over 10 year history of psychiatric problems, died during treatment from non-tegaserod medication overdose
65, woman, Caucasian, (on study drug for 29 days)	Acute myocardial infarction	history of constipation, gastric ulcer and hypothyroidism, died during treatment.
73, woman, Caucasian, on study drug for 10 days	Pulmonary metastases	hospitalized on day 1 for pulmonary metastases of cervical carcinoma, died 120 days after last dose.

IBS patients constitute a vulnerable population for psychiatric events. Two suicides are perhaps not unexpected, but strengthen the signal with respect to "psychiatric events" discussed further below.

Table 13 - Deaths, non-fatal serious adverse events and rare events of potential concern in clinical studies (largest controlled dataset)

Primary system organ class Preferred term	tegaserod N=9269		placebo N=4983	
	% (n)	exposure adjusted rate	% (n)	exposure adjusted rate
Deaths	0.04% (4)	0.18 / 100 yrs	0	0
All non-fatal SAEs	1.37% (127)	5.69 / 100 yrs	1.30% (65)	5.64 / 100 yrs
Any abdominal/pelvic surgeries	0.33% (31)	1.39 / 100 yrs	0.38% (19)	1.65 / 100 yrs
specifically cholecystectomy	0.10% (9)	0.40 / 100 yrs	0.04% (2)	0.17 / 100 yrs
Rectal bleeding	1.05% (97)	4.35 / 100 yrs	1.14% (57)	4.95 / 100 yrs
Colitis	0.04% (4)	0.18 / 100 yrs	0.02% (1) [a]	0.09 / 100 yrs[a]
Ischemic colitis	0	0	1 [a]	0.09 /100 yrs

[a] one patient, from the placebo group, was retrospectively classified by FDA as probable ischemic colitis

Table 14 - Deaths, other serious or clinically significant adverse events or discontinuations (key 4 week safety population)

	tegaserod 2 mg bid N=1119 n (%)	tegaserod 6 mg bid N=4286 n (%)	tegaserod all N=5405 n (%)	placebo N=2937 n (%)
Event type				
Deaths	0	1	1	0
Non-fatal SAEs	4 (0.36)	18 (0,42)	22 (0.41)	15 (0.51)
Clinically significant AEs:				
Discontinuations due to any AEs	70 (6.3)	147 (3.4)	217 (4.0)	74 (2.5)
– discontinuations for diarrhoea	16 (1.4)	55 (1.3)	71 (1.3)	4 (0.1)
– discontinuations for abdominal pain	17 (1.5)	29 (0.7)	46 (0.9)	13 (0.4)
Diarrhoea	87 (7.8)	252 (5.9)	339 (6.3)	73 (2.5)
Abdominal / pelvic surgery	1 (0.09)	3 (0.07)	4 (0.07)	3 (0.10)
Cholecystectomy	0 (0.00)	1 (0.02)	1 (0.02)	0 (0.00)
Rectal bleeding events	4 (0.36)	19 (0.44)	23 (0.43)	12 (0.41)
Colitis	0	0	0	0
Cardiac arrhythmia	9 (0.8)	13 (0.3)	22 (0.4)	9 (0.3)
Hypersensitivity reactions	33 (2.9)	69 (1.6)	102 (1.9)	61 (2.1)

Specific adverse events

- Nervous system (NS):

Table 15 - Frequency of nervous system and psychiatric disorders related adverse events in open long-term studies.

	Teg 2-6 mg bid N =1232 n (%)	Teg 2 mg bid N= 284 n (%)	Teg 6 mg bid N=556 n (%)	All Teg N = 2072 n (%)
Any adverse events				
Nervous system total	412 (33.4)	54 (19.0)	106 (19.1)	572 (27.6)
- CNS total	46 (3.7)	14 (4.9)	15 (2.7)	75 (3.6)
- Nervous system Others	382 (31.0)	45 (15.8)	84 (15.1)	511 (24.7)
- Peripheral NS total	14 (1.1)	7 (2.5)	9 (1.6)	30 (1.4)
Psychiatric Disorders	116 (9.4)	16 (5.6)	50 (9.0)	182 (8.8)

An analysis of the subset of "Nervous system disorders" System Organ Class (SOC) was performed, i.e. on adverse events which neither fulfilled the criteria for CNS- nor peripheral nervous system-related adverse events. This category was named "NS other".

Table 16 - Number (%) of patients with adverse events related to psychiatric disorders in pooled studies in chronic constipation using doses of 2 and 6 mg bid

Preferred Term	Tegaserod 2mg bid n=861	Tegaserod 6 mg bid n=881	Placebo n=861
-Total	37(4.3)	38(4.3)	28(3.3)
Anxiety	4(0.5)	5(0.6)	1(0.1)
Anxiety aggravated	1(0.1)	0(0.0)	1(0.1)
Anxiety disorder	1(0.1)	0(0.0)	0(0.0)
Confusion aggravated	0(0.0)	0(0.0)	1(0.1)
Depressed mood	2(0.2)	0(0.0)	0(0.0)
Depression	6(0.7)	6(0.7)	8(0.9)
Depression aggravated	4(0.5)	1(0.1)	2(0.2)
Depression suicidal	0(0.0)	1(0.1)	0(0.0)
Dissociative disorder NOS	0(0.0)	1(0.1)	0(0.0)
Insomnia	11(1.3)	16(1.8)	12(1.4)
Irritability	0(0.0)	0(0.0)	2(0.2)
Libido increased	1(0.1)	0(0.0)	0(0.0)
Loss of libido	1(0.1)	0(0.0)	0(0.0)
Mood swings	2(0.2)	0(0.0)	0(0.0)
Nervousness	1(0.1)	1(0.1)	1(0.1)
Neurosis NOS	0(0.0)	1(0.1)	0(0.0)
Nightmare	0(0.0)	2(0.2)	1(0.1)
Panic attack	2(0.2)	0(0.0)	0(0.0)
Restlessness	2(0.2)	0(0.0)	1(0.1)
Sleep disorder NOS	1(0.1)	1(0.1)	2(0.2)
Stress symptoms	1(0.1)	4(0.5)	1(0.1)
Tearfulness	1(0.1)	0(0.0)	0(0.0)

Analyses of a US claims database (MarketScan) show that the reported incidence of suicide tendency, suicidal behaviour, depression, anxiety, etc. is approximately doubled for patients with IBS/chronic constipation, irrespective of age, gender, etc. Actually the only covariate not found to be associated with a doubling of the risk in IBS patients was “history of depression” (but the risk in this group was about 10 times higher than in those without a history of depression).

There were a total of 16 post-marketing reports for tegaserod of: suicide (2), attempted suicide (3), suicidal ideation (11). In 13 cases, there were associated risk factors.

As tegaserod is transported by P-glycoprotein (P-gp) in humans, the P-gp expressed in the blood-brain barrier (BBB) is likely to limit the concentration of tegaserod in the brain. A clinical interaction study with the P-gp inhibitor quinidine showed increased exposure (about 70%). There are some safety data from patients exposed to higher doses of tegaserod (12 mg bid n=110) providing similar exposure. The safety data linked with the potential use of P-gp inhibitors, as such, do not indicate an increased risk for common events, but the sample size is too small to exclude relevant differences.

Several single nucleotide polymorphisms (SNPs) have been associated with alterations in expression of the P-gp protein or with the response to known P-gp inhibitors. It is possible that genotypes that are associated with decreased expression of the P-gp protein could result in a greater exposure to the brain, of certain drugs such as tegaserod, due to decreased efflux across the BBB and thus result in an increase in CNS adverse events. To address this question, the applicant performed a pharmacogenetic

analysis on 9 polymorphisms in the P-gp gene for association with psychiatric and CNS-related side effects. The frequencies of adverse events by genotype were similar between the tegaserod and placebo recipients.

There seems to be an increased event rate in the frequency of CNS and psychiatric disorders related adverse events in patients with concomitant treatment with a P-gp inhibitor in the 12-week but not in the 4-week studies. However a temporal relationship between the intake of the co-medication during the study and the observed adverse event is not feasible to assess, as the time point of the co-medication intake was not recorded in most studies (see Table 17).

Table 17 - Frequency of CNS and psychiatric disorders related adverse events in patients with and without concomitant treatment with a P-gp inhibitor, 4- and 12-week studies (Safety population)

	S-Db M1 (4 week studies)				S-Db M2 (12 week studies)			
	Taking same P-GP inhibitor as prior & conmed		Taking no concomitant P-gp inhibitor		Taking same P-gp inhibitor as prior & conmed		Taking no concomitant P-gp inhibitor	
	Teg 6 mg bid N = 373	Placebo N = 103	Teg 6 mg bid N=1984	Placebo N = 687	Teg 6 mg bid N = 281	Placebo N = 279	Teg 6 mg bid N=2778	Placebo N=2726
	n (%)	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)	n (%)
Any adverse events								
NS total	21 (5.6)	7 (6.8)	129 (6.5)	28 (4.1)	56 (19.9)	54 (19.4)	490 (17.6)	471 (17.3)
- CNS	4 (1.1)	3 (2.9)	13 (0.7)	3 (0.4)	14 (5.0)	8 (2.9)	111 (4.0)	113 (4.1)
- NS other	17 (4.6)	5 (4.9)	117 (5.9)	25 (3.6)	48 (17.1)	49 (17.6)	405 (14.6)	383 (14.0)
- Peripheral NS	2 (0.5)	0 (0.0)	3 (0.2)	0 (0.0)	4 (1.4)	3 (1.1)	23 (0.8)	24 (0.9)
Psychiatric	7 (1.9)	1 (1.0)	32 (1.6)	7 (1.0)	18 (6.4)	9 (3.2)	99 (3.6)	94 (3.4)
Severe adverse events								
CNS	0	0	0	0	1 (0.4)	0	14 (0.5)	11 (0.4)
Psychiatric	1 (0.3)	0	0	0	1 (0.4)	0	11 (0.4)	10 (0.4)
Drug related adverse events								
CNS	1 (0.3)	0	8 (0.4)	3 (0.4)	7 (2.5)	2 (0.7)	56 (2.0)	61 (2.2)
Psychiatric	3 (0.8)	0	3 (0.2)	1 (0.1)	4 (1.4)	2 (0.7)	28 (1.0)	17 (0.6)
Adverse events leading to discontinuation								
CNS	0	0	1 (0.1)	1 (0.1)	1 (0.4)	0	17 (0.6)	20 (0.7)
Psychiatric	0	0	2 (0.1)	0	3 (1.1)	0	8 (0.3)	6 (0.2)

Teg = Zelnorm (tegaserod)

At present no consistent pattern associating tegaserod and P-gp inhibition with an increased incidence of adverse events has been identified. As discussed, there might be an association between dose (2 mg bid vs. 6 mg bid), use of P-gp inhibitors and psychiatric events.

Cardiac arrhythmias: There were 4 cases (0.08%) of arrhythmias, including one case of ventricular tachycardia, reported in the tegaserod 4-week safety population vs. none in the placebo groups. Otherwise no differences were seen between placebo and tegaserod in the safety populations. The case of ventricular tachycardia was reported to have occurred after coronary by pass surgery. No other cases of ventricular tachycardia have been reported.

- ECG: New or worsened ECG abnormalities were observed in the 12-week studies in similar incidences in tegaserod and placebo groups - about 10%. Similarly, there were no signals

related to QT-prolongation.

- Hypersensitivity reactions: A total of 271 post-marketing reports of hypersensitivity reactions in patients taking tegaserod have been received. Of these, 38 were serious reaction reports. There does not appear to be any identifiable risk factor beyond possibly a prior history of drug hypersensitivity reactions, atopy, or autoimmune disease, which were reported in 54% of the serious cases in which medical history was provided. Serious reports of hypersensitivity reactions in patients taking tegaserod are rare with a reporting rate of 7.3/100,000 patient years. In the clinical database there were 3 reported cases of hypersensitivity reactions.

- Ischaemic colitis (IC): The association between IBS and IC is acknowledged. There might, however, be a difference between diarrhoea and constipation predominant diseases, both in the sense that cases of IC might be misdiagnosed as diarrhoea predominant IBS (IBS-D) and that anti-diarrhoeal compounds in general or drugs with constipation as side effect might increase the risk for IC. No epidemiological data differentiating between IBS-D and IBS-C have been submitted.

  With respect to duration of therapy and risk for IC, there appears to be no strong relationship, but apparently the risk is not reduced with prolonged therapy as about 50% of the events were reported after 8 weeks or more of therapy while about 30% of the patients used tegaserod for more than 8 weeks.

- Weak signals with respect to myositis and conjunctivitis have also been observed.

- A numerically higher incidence of cholecystectomy has been shown. Therefore an epidemiological study (ZEST) was initiated by the applicant, and the final results were submitted after the conclusion of the CHMP opinion for Zelnorm in December 2005 (within the re-examination procedure).

- Laboratory findings

Haematology: A slightly higher incidence of eosinophilia was observed in the tegaserod arm (1.9%) compared with the placebo arm (1.6%) in the key 4-week safety population. Otherwise, there were no differences. In the re-treatment study no exaggeration of eosinophilia was observed on repeated exposure.

In the 12-weeks studies a higher incidence of ANC ≤1.0 (Absolute Neutrophil Count) was observed in the tegaserod groups than in the placebo groups - 0.6% vs. 0.2%. As in the 4-week studies, more patients with eosinophilia were observed in the tegaserod arms (2.7%, 6 mg bid vs. 1.7%, placebo).

In the pooled safety data base, a seemingly higher incidence of neutropenia was noted in patients treated with doses >12 mg/day, (4/345). The likelihood of a causative association was found to be extremely low and no further actions were considered to be required.

There were no signals with respect to the liver (except for cholecystectomy) and kidney or electrolytes reported in the summary of safety.

- Safety in special populations

Altogether 73 pregnancies were reported in clinical trials, but no evidence of differences in outcome between placebo and tegaserod were identified. These data are too limited to draw conclusions regarding use in pregnancy.

The incidence of adverse events was higher in patients above 65 years of age. In patients above 65 years diarrhoea was observed in 6.9% vs. 5.0% and in those below 65 years 3.9% vs. 1.7%, tegaserod and placebo, respectively.

- Safety related to drug-drug interactions and other interactions

The safety data base has been searched for signals in relation to commonly co-prescribed compounds

in patients with IBS. Only with respect to proton pump inhibitors and H2 antagonists, a higher incidence of gastrointestinal events was found. The results however were similar in the verum and placebo groups.

- Discontinuation due to adverse events

An overview of patient withdrawals for tegaserod 6 mg bid and placebo groups in each pooled safety populations are summarized in the following table.

Table 18 - Patient withdrawals – pooled safety population

Population			Total withdrawals			Reason for withdrawal		
			Total	Women	Men	AE	IE	All others*
(database)	Treatment	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Key 4-week (S-Db1)	Teg 6mg bid	4286	341 (8.0)	318 (7.8) (N=4085)	23 (11.4) (N=201)	112 (2.6)	113 (2.6)	116 (2.7)
	Placebo	2937	207 (7.0)	191 (7.1) (N=2689)	16 (6.5) (N=248)	55 (1.9)	60 (2.0)	92 (3.1)
12-week (S-Db2)	Teg 6mg bid	2188	407 (18.6)	359(18.1) (N=1988)	48 (24.0) (N=200)	155 (7.1)	51 (2.3)	201 (9.2)
	Placebo	2166	377 (17.4)	349(17.8) (N=1958)	28 (13.5) (N=208)	95 (4.4)	69 (3.2)	213 (9.8)
Long-term (S-Db3)	Tegaserod†	1340	562 (41.9)	-	-	122 (9.1)	109 (8.1)	331 (24.7)
Pooled indication	Teg 12 mg/d	5761	795 (13.8)	721(13.5) (N=5355)	74 (18.2) (N=406)	264 (4.6)	185 (3.2)	346 (6.0)
(S-Db5)	Placebo	4435	683 (15.4)	618(15.7) (N=3947)	65 (13.3) (N=489)	170 (3.8)	176 (4.0)	337 (7.6)

AE = adverse event, IE = insufficient efficacy (includes unsatisfactory (therapeutic) effect and treatment failure)
† all Tegaserod doses: range 0.5 to 12 mg bid, mostly 2 or 6 mg bid
* includes withdrawal of consent, lost to follow-up, protocol violation, abnormal laboratory values, administrative problems, subject's condition no longer requires study drug, and undefinded other reasons
Teg = Zelnorm (tegaserod)

Patient withdrawals in the tegaserod group was similar to placebo group. However, adverse events were the most frequent reason for study discontinuation in the tegaserod group compared to the placebo group.

- Post marketing experience

Two main safety aspects emerged from the post marketing surveillance (PMS) database, which led to a modification in the labelling of tegaserod in the USA, in April 2004:

– Serious complications of diarrhoea: By 30 June 2004, events of clinically significant consequences of diarrhoea had been reported in 33 patients (equivalent to 8.5/100 000 patient years). These included rare reports of hypovolemia, hypokalemia, and need for i.v. fluid replacements, but did not involve any diarrhoea-related deaths.

– Ischemic colitis and other ischemic events of the bowel: No cases of ischemic colitis or other ischemic events of the bowel in tegaserod patients have been reported in clinical trials. However on 30 June 2004, there were 32 case reports or 8.2/100 000 patient years from post-marketed use of tegaserod, similar to the incidence of ischemic colitis reported in the general population (7-47/100 000 patient years). The incidence of ischemic colitis in the IBS population (not treated with tegaserod) is estimated to be from 43 to 179 cases per 100 000 patient years.

The possibility for ischemic colitis was added to the US label as a precautionary statement.

- Discussion on clinical safety

Given the benign nature of IBS-C, and the modest effect observed with tegaserod, the safety profile of the compound has to be very favourable.

From some aspects, the safety database is reassuring, e.g. with respect to number of patients. It should be noted, however, that even if the sought indication relates to episodic therapy, median time to recurrence of symptoms was about 4 weeks. Therefore what might in fact be close to long-term use, continuous therapy appears foreseeable in many patients and here the safety database is less reassuring.

Some of the gastroenterology experts that were invited to the CHMP discussion on Zelnorm on 16 November 2005, were also in agreement with the view that long-term data was necessary to demonstrate safety with repeated use (in addition to the maintenance of efficacy).

Two adverse reactions were initially raised as major concerns, namely; clinical significant consequences diarrhoea and hypersensitivity reactions. The incidences of these events have thereafter been defined with acceptable precision.

From a tolerability perspective, obvious adverse reactions relate to the pharmacology of tegaserod, mainly diarrhoea.

After detailed review of uncommon events with a less obvious causal relationship to tegaserod (neutropenia, myositis, conjunctivitis and CNS –related), the remaining main safety concern is CNS-related adverse events, including depression and potential risk for suicidality. It was argued that these signals are weak, inconsistent and that the apparent increase, if any, is small. This, however, should be interpreted from the perspective that these data are derived from clinical studies, where the study effect related to counselling, frequent contact with health personnel, questionnaires, etc. is likely to reduce the risk for depression. Furthermore, IBS patients constitute a vulnerable population with an estimated incidence of suicidality approximately doubled compared with non-IBS patients.

The use of P-gp inhibitors and P-gp polymorphism were discussed in relation to CNS signals. Although the applicant's response was comprehensive, data on pharmacogenomics are hard to interpret without a hypothesis linking certain genotypes to poor function of the blood-brain barrier.

A clinical interaction study with quinidine showed increased exposure of tegaserod (about 70%). There are some safety data from patients exposed to higher doses of tegaserod (12 mg bid n=110) providing similar exposure. The safety data linked with the potential use of P-gp inhibitors, such as quinidine did not indicate an increased risk for common events, but the sample size was too small to exclude relevant differences.

In conclusion the safety profile of Zelnorm (tegaserod) is not devoid of concerns for a benign condition such as IBS-C and the post-marketing signals add to this concern.

2.5 Pharmacovigilance

- Detailed description of the Pharmacovigilance system

The description of the Pharmacovigilance system was provided by the applicant.

- Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan. The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at that time.

2.6 Conclusions, benefit/risk assessment and recommendation prior to appeal

Quality

The design, manufacture, quality control and stability of this product were satisfactory. There were no

unresolved quality issues that could have a negative impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology
In vitro and *in vivo* studies have shown that tegaserod is a specific partial agonist of the 5-HT_4 receptor. In the GIT, it increased motility and tone, and may have some anti-nociceptive activity. Safety pharmacology studies reveal no cause for concern, including cardiovascular safety.

The pharmacokinetic characteristics of tegaserod in the species used for toxicity testing have been described adequately, and it appears that exposure to all identified human metabolites has been achieved in at least one species used in the respective toxicology studies.

No non-clinical concerns were identified in studies of general toxicity, genotoxicity or the rat carcinogenicity study. The intestinal tumours identified in the mouse carcinogenicity study have been discussed in depth, and the applicant has provided reasonable mechanistic support to allow the conclusion that these tumours are not of concern for the intended clinical use of Zelnorm.

Embryotoxicity but no teratogenic effects, was observed. In rabbits, a NOEL cannot be established. Moreover, tegaserod impaired implantation, early embryonic development and reduced pup survival in rats, where the exposure at the LOEL was 8 times the clinical exposure. Peri-post natal development was affected, including reduced pup survival, at maternal exposure levels less than 2 times the clinical exposure and delayed sexual development. The use of Zelnorm during pregnancy and breast feeding should be avoided, and it should not be used in women attempting to conceive.

Efficacy and safety
The pivotal, placebo controlled trial in women with IBS-C, A2306, was designed in agreement with the CPMP within previous Scientific Advice procedures. The primary outcome measures are considered relevant and there was a high degree of consistency in response in primary, secondary and tertiary endpoints. Also in the second period, which studied an enriched population, there was a statistically significant effect. From this perspective the results are considered statistically convincing and robust.

However, the magnitude of the treatment effect did not meet the pre-specified objectives and the clinical relevance of the observed efficacy was seriously questioned by the CHMP. Moreover, in the second period, which studied an enriched population, the effect size was smaller than expected by CHMP from the results in Period 1. Hence, available data do not support maintenance of an effect.

The company is applying for repeated treatment in line with symptomatic treatment of a fluctuating disease. The need for repeated treatment was apparent in the pivotal study where the median time to recurrence of symptoms in responders was about 4 weeks. As long-term treatment is foreseeable in many patients, the lack of long-term data demonstrating sustained activity over several cycles of therapy was considered to be a significant deficiency in the documentation.

In terms of the safety of Zelnorm (tegaserod), CNS/psychiatric events were considered to constitute an outstanding safety issue. This should be added to an albeit low frequency of serious hypersensitivity reactions and clinically significant consequences of diarrhoea and the non-resolved issues related to cholecystitis and ischemic colitis.

Taking all the above into consideration, the CHMP concluded that the demonstrated modest short-term effect of questionable clinical relevance cannot outweigh the known adverse event profile as well as the long-term safety uncertainties. Therefore, the benefit/risk balance for Zelnorm in the proposed indication is unfavourable.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the benefit/risk balance of Zelnorm indicated for the repeated symptomatic short-term treatment of Irritable Bowel Syndrome in women whose predominant bowel habit is constipation

(IBS-C) was unfavourable, and therefore did not recommend the granting of the marketing authorisation.

GROUNDS FOR REFUSAL

Whereas

- the treatment effect, although statistically significant, is not considered clinically relevant
- the effect size in the enriched population in the second period of treatment was lower than expected, not supporting maintenance of effect
- the known adverse event profile as well as long-term safety uncertainties

the CHMP recommended the refusal of the granting of the Marketing Authorisation for Zelnorm at the December 2005 CHMP meeting.

RE-EXAMINATION OF THE CHMP OPINION OF 14 DECEMBER 2005 FOR ZELNORM

At the December 2005 CHMP meeting following discussion of the Marketing Authorisation Application for Zelnorm, the CHMP had concluded that the overall benefit/risk for Zelnorm in the symptomatic treatment of women with IBS-C was unfavourable.

On 22 December 2005, the applicant submitted written notice requesting a re-examination, and the detailed grounds for the re-examination request were submitted on the 17 February 2006.

Written responses to various safety and efficacy comments in the Appeal Assessment Reports were submitted on 10 March 06.

An ad hoc expert group meeting was held on 15 March 2006 in preparation of the CHMP meeting on 20-23 March 2006, and the conclusions of the expert group were:

- The definition of severity proposed by the applicant, and the identification of patients with 'severe' IBS were not seen to be feasible in clinical practice. Furthermore the definition of severity was not seen to reflect the actual burden of severity and was considered likely to cause difficulties in clinical practice. It was therefore agreed that the restriction of the indication of Zelnorm to 'severe IBS' would not be meaningful, and that consideration of the overall population as initially presented by the applicant, would be preferable.

- It was acknowledged that the results seen with the 75% rule (i.e. an improvement over 3 out of 4 weeks) although small were consistent to the extent that the endpoints measured, were fairly stringent. Although the ~ 10% difference was admittedly low and less than the proposed 15%, this was nevertheless a significant effect.

  Bearing in mind the weaknesses of the IBS-QoL questionnaire used, the effect seen was thought unlikely to be significant. Although the QoL measures used were only tertiary efficacy endpoints (predefined), it was agreed that they could have supported the clinical relevance of the weak primary endpoint results, had they been convincing.

- It was recognised that the patient populations included in Period 1 and Period 2 were not the same. Nevertheless the effect observed with Zelnorm in Period 2 is undoubtedly significant (statistically). It was noted that there appeared to be no sustained effect once treatment with Zelnorm had been stopped.

It had been noted earlier during the discussion that there was no loss of efficacy on re-treatment of the partially enriched population in Period 2. Overall the experts concluded that although the efficacy of Zelnorm was low, there were currently no safety concerns that could be identified.

The applicant gave oral explanations at both the ad hoc expert group meeting and at the CHMP meeting.

Grounds for refusal 1: the treatment effect, although statistically significant, is not considered clinically relevant:

Applicant's position

Study A2306 showed statistically significant and consistent efficacy of tegaserod during both initial treatment (Period 1) and re-treatment (Period 2) on the primary and co-primary outcome variables using the predefined response definition (75% rule).

In order to optimize the benefit/risk of the treatment, the applicant proposed to restrict the use of tegaserod to the IBS-C population with highest need of therapy, i.e. those with severe abdominal pain/discomfort and/or severe abdominal bloating.

- In patients with severe abdominal discomfort/pain at baseline (Table 19), the therapeutic gain over placebo in Period 1 was 13.5% and 12.9% (75% rule) for the primary and the co-primary variables respectively. Using the 50% rule, which is the current CHMP recommendation (CPMP/EWP/785/97), the therapeutic gain over placebo in Period 1 was 17.7% (overall relief) and 16.6% (abdominal discomfort/pain) (all $p<0.001$).

- In patients with severe abdominal bloating at baseline (Table 20), the therapeutic gain in Period 1 was 13.7% and 11.8% (75% rule) for the primary and the co-primary variables respectively. Using the 50% rule, the therapeutic gain in Period 1 was 18.5% (overall relief) and 15.0% (abdominal discomfort/pain) (all $p<0.001$).

Table 19 Summary of results of efficacy variables during Period 1 and Period 2 in patients with severe abdominal discomfort/pain at baseline (study A2306)

	Period 1				Period 2			
Measurement	Tega 6 mg bid N= 927 (%)	Placebo N=227 (%)	Diff (%)	p-value	Tega 6 mg bid N= 184 (%)	Placebo N=207 (%)	Diff (%)	p-value
Primary efficacy variables								
Relief of overall symptoms	35.5	22.0	13.5	0.0003	46.2	30.9	15.3	0.0024
Relief of abdominal discomfort/pain	34.0	21.1	12.9	0.0005	45.1	28.5	16.6	0.0002
Secondary efficacy variables								
Relief of overall symptoms (50% rule)	52.5	34.8	17.7	<0.0001	63.6	46.4	17.2	0.0010
Relief of abdominal discomfort/pain (50% rule)	50.1	33.5	16.6	<0.0001	60.3	43.0	17.3	0.0006
Improvement in abd. discomfort/pain (EOT)	64.1	50.7	13.4	0.0006	69.3	59.9	9.4	0.0396
Improvement in bloating (EOT)	60.9	44.8	16.1	<0.0001	68.2	57.3	10.9	0.0131
Relief of constipation (75% rule)	40.7	22.9	17.8	<0.0001	44.6	28.5	16.1	0.0007
Tertiary efficacy variables								
Quality of Life (IBS-QoL)	14.2	11.4	2.8	0.1904	NA	NA	NA	NA
Satisfaction with study medication	39.1	24.6	14.5	<0.000	51.9	41.2	10.7	0.013
Study medication relief; expectations for IBS symptoms	26.9	15.1	11.8	<0.0001	41.3	31.1	10.2	0.0337
Better relief of study medication vs previous medication	58.8	47.5	11.3	0.0054	75.9	59.1	16.8	0.0101

Diff = difference between tegaserod and placebo
Tega = Zelnorm (tegaserod)

Table 20 Summary of results of efficacy variables during Period 1 and Period 2 in patients with severe bloating at baseline (study A2306)

	Period 1				Period 2			
Measurement	Tega 6 mg bid n= 1118 (%)	Plac N=276 (%)	Diff (%)	p-value	Tega 6 mg bid N= 232 (%)	Plac N=244 (%)	Diff (%)	p-value
Primary efficacy variables								
Relief of overall symptoms	34.0%	20.3%	13.7	<0.0001	44.8	29.5	15.3	0.0007
Relief of abdominal discomfort/pain	32.1%	20.3%	11.8	0.0002	42.7	27.5	15.2	0.0002
Secondary efficacy variables								
Relief of overall symptoms (50% rule)	51.1%	32.6%	18.5	<0.0001	62.5	44.7	17.8	<0.0001
Relief of abdominal discomfort/pain (50% rule)	48.7%	33.7%	15.0	<0.0001	57.8	40.6	17.2	<0.0001
Improvement in abdominal discomfort/pain (EOS)	59.5%	43.3%	16.2	0.0036	63.9	59.9**	9.4	0.0396
Improvement in bloating (EOS)	59.9%	45.6%	14.3	0.0129	68.1	51.9	16.3	<0.0001
Relief of constipation (75% rule)	39.4%	21.4%	18.0	<0.0001	44.4	28.3	16.1	0.0002
Tertiary efficacy variables								
Quality of Life (IBS-QoL)	13.6	10.9	2.7	0.0423	NA	NA	NA	NA
Satisfaction with study medication	37.5	23.6	13.9	<0.0001	52.8	37.6	15.2	0.0001
Study medication relief; expectations for IBS symptoms	26.2	15.9	10.3	<0.0001	42.6	27.1	15.5	0.0002
Better relief of study medication vs previous medication	58.3	47.3	11.0	0.0080	74.5	55.8	18.7	0.0006

Diff = difference between tegaserod and placebo
Tega = Zelnorm (tegaserod)

In order to limit the use of Zelnorm (tegaserod) in patients who are unlikely to respond to treatment, the applicant proposed to recommend in the Summary of Product Characteristics (SPC) that treatment should be stopped in patients who do not have satisfactory relief of IBS symptoms after they have been treated for 2 weeks.

CHMP position:
The CHMP was of the opinion that the restriction of the indication of Zelnorm (tegaserod) to 'severe IBS' would not be meaningful, and that consideration of the overall population as initially presented by the applicant, would be preferable and should be kept. This was in line with the view of the experts that the definition of severity proposed by the applicant, and the identification of patients with 'severe' IBS were not seen to be feasible in clinical practice. Furthermore the definition of severity was not seen to reflect the actual burden of severity and was considered likely to cause difficulties in clinical practice.

As regards the measured clinical effect, the experts acknowledged that the results for the overall population seen were small although statistically significant - 9.3% difference for the overall relief of symptoms and 9.1% difference for relief of abdominal discomfort/pain. This effect was based on the 75% rule (i.e. an improvement over 3 out of 4 weeks), which was considered to be fairly stringent and more conservative than current CHMP Points to Consider document.

However based on the discussion at the expert meeting and the assessment reports from the Rapporteurs, the CHMP remained concerned regarding the high placebo response rate observed in both the 'severe'

subgroup and in the overall patient population, and affecting both treatment groups. This remained a major cause for concern. In fact for the primary efficacy endpoint - relief of overall symptoms – the percentage of response seen in Period 1 was 33.7% in the tegaserod group and 24.2% in the placebo group. Similarly for the primary co-endpoint relief of abdominal discomfort/pain a response of 31.3% was seen for the tegaserod group and 22.1% in the placebo group in Period 1. The CHMP did not consider the differences in effect compared to placebo to be relevant and as such did not represent a sufficient demonstration of efficacy.

The CHMP in agreement with the experts considered that QoL is an important issue in IBS. Bearing in mind the weaknesses of the IBS-QoL questionnaire used, the expert's views were that the effect seen was unlikely to be significant. Although the QoL measures used were only tertiary efficacy endpoints (predefined), it was agreed that they could have supported the clinical relevance of the weak primary endpoint results, had they been convincing. The CHMP considered that while IBS is known to have a major influence on the QoL of these patients, Zelnorm (tegaserod) was not shown to influence IBS-QoL. The CHMP agreed that the QoL results did not contribute to demonstrate a benefit of the drug.

Grounds for refusal 2; the effect size in the enriched population in the second period of treatment was lower than expected, not supporting maintenance of effect

Applicant's response:
Further to the inclusion of responders, patients with only a partial response (those without response for one of the two outcome variables) were also allowed to undergo re-treatment. Thus the Period 2 population was at most only partially enriched. Responder rates in study A2306 for both primary and co-primary outcome variables showed that the partial enrichment design leads to an increased effect with repeated treatment from approximately 9% in Period 1 to 16-17% in Period 2.

In the subpopulation with severe abdominal discomfort/pain at baseline, the magnitude of effect in Period 2 met or exceeded the criteria of ≥ 15%, using both the 75% and the 50% rule.

CHMP's position:
It was recognised that the patient populations included in Period 1 and Period 2 were not the same. It was also recognised that symptom pattern and intensity may vary over time, especially in a disorder such as IBS. While it is acknowledged by the CHMP that in Period 2 Zelnorm (tegaserod) has a statistically significantly different effect from placebo and that the magnitude of this difference is numerically higher than in Period 1, a marked loss of responders is observed among patients having responded to the first treatment cycle. Although it is acknowledged that the expected variability in the placebo response may have played a role in this finding, in a treatment with such a high placebo component this would lead to a large loss of the responders over repeated cycles. This supports the CHMP conclusion regarding grounds for refusal no. 1.

Grounds for refusal 3; the known adverse event profile as well as long-term safety uncertainties

Applicant's response:
Severe hypersensitivity and CSC-diarrhoea are identified risks, whereas psychiatric disorders, gallbladder/abdominal surgery, and ischaemic colitis have been acknowledged as potential risks, even though extensive studies did not reveal an association with tegaserod therapy. The final results of the ZEST study did not reveal any evidence for an increased risk of either abdominal/pelvic surgery or gallbladder surgery amongst patients who used tegaserod. In addition, the CHMP concern that severe diarrhoea might be a sign of IC was not confirmed in a comprehensive database search performed by the applicant.

To date, over 14,000 patients have been exposed to tegaserod in clinical trials. Eight hundred patients have been continuously exposed to tegaserod for 12 months or more and at least half of these have received tegaserod at the recommended dose of 6 mg b.i.d. More than 1,000 patients were treated continuously for at least 6 months at 6 mg b.i.d. Furthermore, an estimated 2.5 million patients have been prescribed tegaserod, corresponding to an exposure duration of 640,215 patient–years (April 30, 2005). The post-marketing safety profile of tegaserod, based on the most recent data (Nov 30, 2005;

921,206 patients-years), is unchanged from the one based on the previous cut-off (April 30, 2005). This extensive database did not suggest that tegaserod was unsafe during short- or long-term treatment.

CHMP position:
The CHMP concluded that the safety profile had been adequately characterized for the claimed use.

CHMP overall conclusion on benefit/risk
Having considered the response from the applicant, the discussion during the ad hoc expert group meeting and the CHMP members and experts discussion during the oral explanation, the CHMP, by majority (with 11 divergent opinions), was of the opinion that the benefit/risk for Zelnorm (tegaserod) in the claimed indication was not considered positive.

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