REVIEW ARTICLE

Drug Safety 2004; 27 (4): 229-242
0114-5916/04/0004-0229/$31.00/0

Benefit-Risk Assessment of Tegaserod in Irritable Bowel Syndrome

Richard Lea and *Peter J. Whorwell*

Medical Academic Department, South Manchester University Hospitals, Manchester, United Kingdom

Contents

Abstract

Tegaserod is a new partial agonist of serotonin 5-HT_4 receptors specifically developed for the treatment of nondiarrhoeal forms of irritable bowel syndrome (IBS). Among its various effects is the stimulation of the peristaltic reflex with its promotility action appearing to affect the whole length of the gastrointestinal tract. Tegaserod has been assessed in a number of international multicentre trials and its use leads to an improvement in abdominal pain and bowel dysfunction as well as global well-being, at the expense of remarkably few adverse effects. It is noteworthy that it also appears to improve bloating, a benefit that has not been previously reported for a medication used in IBS. The optimal dose is 6mg twice daily and the advantage of tegaserod over placebo in different trials varies from 5–20% with the number needed to treat ranging from 5–15 depending on the time at which this effect is calculated during the course of a trial. Recent experience with other drugs acting on 5-HT receptors has focused attention on possible safety issues such as prolongation of the QTc interval on the electrocardiogram and ischaemic colitis. However, data from efficacy trials and studies specifically designed to address the safety of tegaserod have not revealed any evidence of cardiotoxicity or the

potential for causing ischaemic colitis. Furthermore, investigation of possible interactions with other drugs such as warfarin or the oral contraceptive have not resulted in any prescribing restrictions. Inappropriate prescription of tegaserod to a subgroup of IBS patients for which the drug was not designed, does not appear to have any serious consequences. Most of the efficacy data on tegaserod has been accumulated in females, simply as a result of the failure to recruit adequate numbers of males or restriction of trials to females. There is therefore insufficient information to assess whether there might be any potential gender differences in responsiveness. For this reason, the drug is currently only licensed for use in females.

Irritable bowel syndrome (IBS) is the most frequently encountered condition in hospital gastroenterological practice[1,2] and accounts for >10% of community practice visits.[3] The condition affects approximately 10% of the Western population with a female to male predominance of approximately 2 : 1.[4] The diagnosis is based on satisfaction of established symptom-based diagnostic criteria, of which several exist,[5-7] together with limited investigation to exclude other diseases.[8] The syndrome can be classified as diarrhoea-predominant, constipation-predominant or alternating subtypes depending on the predominant bowel habit. Prevalence rates and gender ratios are generally similar among different subtypes of IBS, except that the constipation-predominant IBS is more common among females than males.[9]

The majority of patients with IBS report at least one symptom on most days. Although the severity of symptoms may vary, the disease frequently causes clear impairment in quality of life and often loss of normal social functioning.[10] Indeed, quality of life may be impaired to a similar degree to serious chronic diseases such as dialysis-dependent renal failure.[11] Treatment has always been unsatisfactory, and has traditionally involved using individual drugs targeted at particular symptoms, frequently resulting in polypharmacy. Over the past few years, several new drugs modulating serotonin receptors have been developed that offer the possibility of improving the multiple symptoms of IBS with one treatment. The first of these to reach the marketplace was alosetron, a serotonin 5-HT_3 receptor antagonist, and subsequently tegaserod a 5-HT_4 receptor partial agonist. This review will focus on tegaserod paying particular attention to the benefits and risks of treatment.

1. Serotonin and Receptors

Serotonin is an important neurotransmitter in the brain gut axis and its actions are reviewed in detail elsewhere.[12] Ninety-five percent of serotonin in the body is found within the gastrointestinal tract, primarily within the enterochromaffin cells. The physiological effect of the molecule is complex since this depends on activation of seven different classes of receptors with at least 21 subtypes. In the gut 5-HT receptors are present on gut neurones, smooth muscle cells and enterochromaffin cells, and of these the most important are the 5-HT_3 and 5-HT_4 receptors.

Stimulation of the 5-HT_3 receptor may result in smooth muscle contraction or relaxation, depending on whether excitatory or inhibitory neurotransmitters are released. It also results in fluid and electrolyte secretion into the gut lumen. Additionally, 5-HT_3 receptors may have a role in visceral sensation, since receptors are present on vagal and spinal afferents, and in the control of vomiting since receptors are also present in central emesis centres.

In the gut, 5-HT_4 receptors are present within the myenteric plexus, smooth muscle cells, enterochromaffin cells, and primary afferent nerves. Activation results in modulation of the peristaltic reflex and fluid and electrolyte secretion.[13] The 5-HT_4 receptors are also present in the heart[14] (where they mediate an increase in heart rate and the force of

atrial contraction), the adrenal cortex (where they increase aldosterone secretion),[15] and in the bladder (where they mediate an increase in detrusor tone).[16]

As is true of all transmitters, an efficient removal mechanism for 5-HT is necessary following release of the molecule, in order to prevent continuous activation of its associated receptors. Since 5-HT is highly charged it does not readily cross plasma membranes, which is necessary for intracellular deactivation to occur, and this process is facilitated by specialised transporter proteins. Although there are several of these, the most important is the serotonin reuptake transporter protein (SERT), which is inhibited by the selective serotonin reuptake inhibitor and tricyclic group of antidepressants. Recent reports have identified differences in the genotypes coding for SERT in patients with diarrhoea- and constipation-predominant subtypes of IBS,[17] and have also suggested a role for genetic polymorphisms in the SERT promoter region in influencing the response to serotonergic receptor modulating drugs in IBS patients.[18]

2. Drug Trials in Irritable Bowel Syndrome

Early treatment trials in IBS have been criticised for methodological shortcomings.[19] Many of these were conducted over a short period of time and involved only small numbers of patients. However for many reasons IBS is an inherently difficult condition in which to study the effects of therapy. First of all, until recently, a lack of accepted criteria for the diagnosis of IBS has resulted in a heterogenous patient population being enrolled into some studies. Symptoms of the condition tend to be multiple and naturally fluctuate over time; thus, validated outcome measures were poorly defined. The placebo response of up to 80% is notoriously high, and sometimes surprisingly long lasting.[20,21] Finally there is a high patient drop-out rate in many studies, i.e. up to 60% in some studies.[22] These difficulties, which make treatment effect difficult to substantiate, have recently been addressed by an international expert committee which has formulated guidelines for the investigation of treatments in functional gastrointestinal disorders.[22] The recent trials assessing efficacy of the serotonin-receptor modulating drugs have been conducted in accordance with these guidelines.

3. The History of Serotonergic-Modulating Drugs

Cisapride was one of the first serotonergic-modulating drugs to be introduced specifically targeted at the gut. At the time of its launch the mechanism of action had not been defined, although it subsequently became clear that the drug antagonised 5-HT_3 receptors and also acted as an agonist on 5-HT_4 receptors. Cisapride accelerated gastric emptying, enhanced gastric accommodation and reduced intestinal transit time[23] and was mainly used as an adjunct in treating gastro-oesophageal reflux disease, but the drug also found a place in the therapy of functional dyspepsia and of IBS, achieving annual sales in excess of $US1 billion.[24] By the late 1990s, concern was being raised over the potential for cisapride to cause serious ventricular arrhythmias via a mechanism involving prolongation of the QT interval of the ECG secondary to blockade of the rapid component of the delayed potassium rectifier channel in cardiac ventricular myocytes. By 1999 when the drug was essentially withdrawn, there had been reports of over 300 cases of arrhythmias and of 80 deaths.[24]

Alosetron is a potent 5-HT_3 receptor antagonist, which is capable of increasing small bowel fluid and electrolyte absorption[25] and slowing intestinal transit in humans.[26] There is also some laboratory evidence of visceral analgesic properties in animals.[27] Alosetron was approved by the US FDA in February 2000 for the treatment of diarrhoea-predominant IBS in females. However, a number of episodes of ischaemic colitis had occurred in patients taking the drug in the prelicensing trials, and by November 2000 70 serious adverse events had been reported, including 49 cases of ischaemic colitis.[24] Of these, 34 patients were hospitalised, ten required surgery and five died. It eventually became clear that approximately one case of ischaemic colitis occurred for every 700–1000 patients prescribed

alosetron, whilst severe constipation requiring surgery affected about 1 in 10 000 people taking the drug.[13] In November 2000, Glaxo Wellcome voluntarily withdrew alosetron from the market; however, it has recently been reintroduced on a restricted basis.

Subsequent to these major set backs no other 5-HT_3 antagonist has yet reached the marketplace. However, tegaserod, which acts only on the 5-HT_4 receptor and not the 5-HT_3 receptor, is now licensed in some countries. Prucalopride, renzapride, mosapride and cilansetron are all 5-HT active drugs, which remain in varying stages of development.

4. Chemical Nature and Development of Tegaserod

Tegaserod is the first of a new class of compounds called the aminoguanidine indoles. Tegaserod, also called HTF919 (Zelmac®[1] or Zelnorm®) was modelled on serotonin and retains a similar molecular structure. The alkylamine side chain was restricted to make the drug more selective, the primary amine was replaced with a basic moiety to give the drug stability against metabolic degradation and a high molecular polarity was incorporated to avoid penetration into the CNS.[28]

Tegaserod is a selective 5-HT_4 receptor partial agonist, and has no effect on 5-HT_3, muscarinic, adrenergic, dopaminergic or opiate receptors.[29] Compared with serotonin, which has 100% intrinsic activity, tegaserod possesses 21% activity.[29] A partial agonist is capable of submaximal stimulation of a receptor and may displace a full agonist through competitive inhibition. Theoretically this partial agonist activity may be beneficial because of a reduced tendency to produce receptor desensitisation, which could lead to tachyphylaxis, or to the development of tolerance. In addition, a partial agonist may act as an antagonist when receptor occupancy with the endogenous ligand is high, and as an agonist when the occupancy is low.[30] Thus, a partial agonist may also be preferable because it provides a balanced modulation of 5-HT_4 receptors, and is therefore more likely to normalise gut function.[31,32]

5. Mechanism of Action

Tegaserod stimulates the peristaltic reflex via a mechanism involving activation of gut intrinsic primary afferent neurons, which act to relay sensory information from the mucosa to inter-neurons with connections to gut motor neurones.[33] Cephalad smooth muscle contraction is initiated via excitatory inter-neurones using acetylcholine and substance P, whilst caudad smooth muscle relaxation is permitted via inhibitory inter-neurones using vasoactive intestinal polypeptide, pituitary adenyl cyclase-activating peptide or nitric oxide. The net effect is stimulation of peristalsis and augmented motility. Additionally tegaserod promotes chloride and water secretion in the large intestine,[34] which could result in a softening of stool consistency.

6. Preclinical Studies Using Tegaserod

Experiments conducted in animals have demonstrated that tegaserod possesses potent pro-motility actions affecting the whole of the gastrointestinal tract. For example, studies in dogs have shown a dose-dependant stimulation of gastric, small intestinal and colonic motility,[35] and complete reversal of experimentally induced impaired gastric emptying in rats and of impaired colonic motility in mice.[29] A study in cats, which measured firing rates of spinal afferent nerves during gut distension, suggested that tegaserod may also act as a visceral analgesic,[36] a view which has been supported by a recent study in healthy human volunteers.[37]

Preclinical safety pharmacology data were initially collected from anaesthetised and conscious dogs. Tegaserod had no effect on blood pressure, heart rate or respiration and led to no ECG abnormalities.[28] Using isolated Langendorff-perfused rabbit hearts as a model, one study assessed the effect of cisapride, erythromycin and tegaserod on cardiac repolarisation. Unlike cisapride, tegaserod had no effect on the QT interval of the ECG in doses

1 The use of trade names is for product identification purposes only and does not imply endorsement.

up to 500- to 5000-fold higher than the clinical dose.[38] Although plasma levels of cortisol and prolactin may be increased after high doses of tegaserod, this is unlikely to occur at therapeutic doses, and no changes in other pituitary or sex hormones, or in blood glucose levels have been observed in rats administered the drug.[28]

Toxicity studies have been carried out in a variety of laboratory animals.[28] No chronic toxicity was observed following administration of quantities at least 30-fold higher than the equivalent human therapeutic dose in mice, rats or dogs. The LD_{50} (that is the lethal dose for 50% of the animals studied if all of the drug were to be given simultaneously) was over 1300-fold higher than the equivalent human therapeutic dose. In rats there were no effects on fertility or on pre- and post-natal development at 10-fold higher than the equivalent human dose. Approximately 30 human females have become pregnant whilst taking tegaserod, all subsequently delivering normal babies;[28] however, it is known that tegaserod crosses in to breast milk, and therefore should be avoided by lactating females.[28] Tegaserod has now been granted a pregnancy category B by the FDA.

7. Pharmacokinetic Studies in Humans

Tegaserod is rapidly absorbed following oral administration, reaching peak plasma concentration about 1 hour after ingestion. Absorption after oral administration is reduced following ingestion of food (by about 40–65%) and in the presence of acid (approximately 20% of the administered drug undergoes acid hydrolysis in the stomach).[39] Multiple administration follows a dose-proportional pharmacokinetic profile, with no evidence of accumulation.[40] Following absorption tegaserod is 98% plasma protein bound and is widely distributed throughout the body (volume of distribution at steady state of 368 ± 223L), although little passes through the blood brain barrier which limits central adverse effects.[39] Tegaserod has an estimated terminal elimination half-life of 11 ± 5 hours and approximately two-thirds of ingested drug is excreted unchanged in the faeces.[39] The hydrolytic compound and the unchanged form of tegaserod are eventually excreted after glucuronidation in the urine, the main metabolite being 5-methoxyindole-3-carboxylic acid glucuronide.[39] There is no evidence of accumulation of the standard dose in the elderly or in patients with liver cirrhosis or severe renal failure;[31] however, a prudent approach is clearly indicated in patients with advanced co-morbidity.

8. Drug Interaction Studies

Several drug interaction studies have been performed. One of these, which co-administered warfarin and tegaserod in a randomised, open-label crossover study involving 12 healthy volunteers, reported no significant changes in mean or maximal prothrombin times.[41] A trial with oral contraceptives was conducted in healthy women across three menstrual cycles using a randomised, placebo-controlled crossover design. Coadministration of tegaserod did not affect ethinylestradiol, but did result in an 8% decrease in systemic exposure to levonorgestrel; however, this was not felt likely to cause a clinically relevant reduction in contraceptive efficacy.[42] Digoxin was also assessed for an interaction with tegaserod, employing a study protocol resembling that used for warfarin. Slightly reduced plasma concentrations of digoxin were noted during coadministration of the two drugs,[43] although again this was also not thought to be clinically relevant. A study in 18 healthy volunteers randomised to receive either tegaserod or theophylline using a crossover design found a reduced conversion of theophylline to 1-methyluric acid, which was not thought to be clinically relevant, but no other important changes in clearances were seen when both drugs were given, compared with theophylline given alone.[44] Finally a study of similar design was carried out with dextromethorphan (a prototype substrate for cytochrome P450 2D6 enzymes that metabolise drugs such as fluoxetine and omeprazole) in 18 healthy volunteers and found no evidence of a significant interaction.[41]

9. Clinical Studies

Two early studies were carried out in patients with IBS, a dose-ranging study (B251)[45] and a dose-titration study (B202),[46] both using tegaserod 0.5mg, 2mg, 6mg or 12mg twice daily for 12 weeks, but neither has yet been published in full. Results from these studies indicated that the use of tegaserod was associated with an improvement in overall gastrointestinal symptoms. The optimal dosages appeared to be 2mg and 6mg given twice daily, and these were chosen for further evaluation.

Design of the major efficacy trials for tegaserod have complied with recommendations on the design of treatment trials for functional gastrointestinal disorders made by the Rome international working team.[22] The quality of these studies was considered to be very high when judged by agreed standards of assessing clinical trials.[47] They were all randomised, placebo-controlled trials carried out both in hospital and community settings, in Europe, North America and Australasia, and included only patients meeting Rome diagnostic criteria.[7] Following a placebo-free run-in period, a full 12 weeks of treatment with tegaserod or placebo was given, and the primary endpoint was clearly defined using the subjective global assessment (SGA) of relief. Two studies, B351[48] and B301[49] used doses of tegaserod 2mg or 6mg twice daily, compared with placebo, and a third study, B358,[50] compared placebo with a fixed dose of tegaserod 6mg twice daily (since the first two studies had concluded that this was the most effective dose). This study also included a 4-week treatment withdrawal observation period to assess the effect of stopping the drug. Another study, B307[28] used a dose-titration protocol involving either placebo, tegaserod 2mg twice daily, or if there had been no response to this dose after 4 weeks, then tegaserod 6mg twice daily. Recently, a fifth study in an Asia-Pacific population has been published which differed in design from the previous phase III trials.[51] In this study tegaserod 6mg twice daily was given for 12 weeks, although the run-in period was only 2 weeks and the washout period was 4 weeks.[51] This study used a different SGA with a different endpoint as discussed in section 9.1.

9.1 The Subjective Global Assessment

The SGA reflects the patients own assessment of their condition, and can be applied to overall well-being, which was considered the primary outcome variable in the phase III studies, or particular symptoms such as abdominal pain/discomfort and satisfaction with bowel habit. The SGA of relief involves asking subjects to respond to the following question: "Please consider how you felt this past week in regard to your IBS, in particular your overall well being, and symptoms of abdominal discomfort, pain and altered bowel habit by choosing one of the following responses: (i) completely relieved; (ii) considerably relieved; (iii) somewhat relieved; (iv) unchanged; or (v) worse". The SGA for relief was measured weekly. Supplementary indices of abdominal pain or discomfort, bloating and stool frequency/consistency were also assessed daily. The Asia-Pacific study[51] used a different SGA which required subjects to give a binary response of 'yes' or 'no' to the question: "over the past week do you consider that you have had satisfactory relief from your IBS symptoms?"

Global parameters of IBS, such as the SGA for relief have been recommended for use in clinical trials because they are able to capture the multiple symptoms of IBS in a single measure.[52] Although measurement of individual symptoms is useful, it may not accurately reflect an overall change in symptomatology because of the fluctuating course of IBS over time.[52] The SGA of relief has been well validated and an improvement in the SGA correlates with an improvement in secondary endpoints such as abdominal pain and stool frequency and consistency.[49,53]

9.2 Definition of a Responder to Tegaserod

Early efficacy trials defined a responder as an individual who obtained at least considerable relief as judged by their SGA score for at least 2 of the final 4 weeks of the treatment period, or as an individual whose symptoms were at least somewhat

relieved for all of the final 4 weeks. In addition, a monthly responder could be defined as a positive response to tegaserod for any given 4-week treatment period, measured in the same way. In order to be classified a responder, laxative use was restricted to <5 days during the treatment period and not at all for the final 4 weeks. However, since in reality patients with constipation frequently use laxatives, it could be argued that this restraint, which was necessary to make clear the effect of tegaserod, was too rigorous for generalisation to constipated IBS patients in clinical practice and could reduce the therapeutic gain.

The Asia-Pacific study used a binary endpoint, assessing the response to tegaserod during weeks 1–4, and a secondary endpoint as the response over weeks 1–12.[51]

9.3 Tegaserod Efficacy

All phase III trials included large numbers of patients, the majority of whom were female (approximately 85%), and study B358[50] exclusively enrolled females. Thus, there have been some concerns over the extrapolation of these results to male patients. The study populations were similar in terms of symptoms and disease duration, and were felt to be representative of typical IBS patients seen in clinical practice, being drawn from both hospital and community practice. Interestingly, although significant diarrhoea in the 3 months prior to the studies was an exclusion criterion, almost 15% of the patients in study B301 had diarrhoea as part of their IBS symptoms during the baseline observation period, illustrating the propensity for IBS symptoms to alter over time. This characteristic is well appreciated, and inclusion of these patients is valuable in assessing the applicability and safety of tegaserod in real clinical practice.

Results from study B301[49] showed a significant improvement in overall IBS symptoms measured by the weekly SGA with both tegaserod 2mg and 6mg twice daily as compared with placebo. At endpoint, as measured by the last 4-weekly SGAs of relief, the response rates were 46.5% for tegaserod 2mg twice daily, 46.3% for tegaserod 6mg twice daily and 34.5% for placebo ($p < 0.01$). This translates into a treatment benefit of 12% for tegaserod 2mg twice daily and 11.8% for tegaserod 6mg twice daily, which was seen as early as week 1 and sustained through the 12 weeks of treatment duration. In clinical practice this would suggest a response rate to treatment with tegaserod of around 50%. The responder rates at endpoint for the SGA of abdominal pain/discomfort were 29.8% for tegaserod 2mg twice daily, 29.9% for tegaserod 6mg twice daily and 22.6% for placebo ($p = 0.055$ and $p = 0.044$ compared with placebo, respectively). The individual symptoms of abdominal pain or discomfort and stool frequency/consistency that were measured daily also improved significantly across most weeks of the treatment period, and there was also a non-significant trend toward a reduction in the number of days with significant bloating. In this study the major difference between the two active dosages was that tegaserod 6mg twice daily delivered more consistent benefit over time and across the range of IBS symptoms compared with tegaserod 2mg twice daily.

Study B358,[50] the largest therapeutic trial of tegaserod, found a similar beneficial effect from the drug; 43.5% of patients taking tegaserod responded to treatment, compared with 38.8% of patients using placebo ($p = 0.03$). Further analysis revealed that when patients who reported benefit from treatment but had used laxatives were included as responders, higher response rates of 48.3% for tegaserod and 41.7% for placebo ($p < 0.01$) were observed. The weekly SGAs for abdominal pain/ discomfort and bowel habit improved significantly for nearly all weeks of the treatment period and daily symptoms of pain/discomfort, stool consistency/frequency, bloating and straining also showed significant improvements at endpoint. These effects were seen as early as the first week of treatment, persisted whilst treatment was taken and disappeared rapidly after treatment withdrawal, although did not return to pretreatment levels within the 4-week washout period. The number of patients requiring treatment (number-needed-to-treat; NNT) with tegaserod to improve the symptoms of one, was 7.0 during the

first 4 weeks of treatment, 13.3 during the second 4 weeks and 17.1 for the final 4 weeks.

The placebo response was high in both studies[49,50] and this is a well recognised phenomenon in IBS treatment trials. One review, which included 25 controlled trials in patients with IBS, found a median placebo response of 47% which is similar to both these studies.[21] The placebo response is frequently thought to taper off after a period of approximately 12 weeks;[21] however in study B358[50] the placebo response increased over time from 41% at week 1 to 61% at week 12, which reduced the comparative efficacy of tegaserod at the end of the study. This appears to be in agreement with a recent report examining the efficacy of alosetron in IBS, which reported a sustained response to placebo that persisted even as long as 12 months.[20] Nevertheless, the placebo response is difficult to separate from the spontaneous short-term resolution of symptoms that is characteristic of functional gastrointestinal diseases.

Studies B301,[49] B358[50] and the Asia-Pacific study[51] are all placebo-controlled trials of tegaserod that have been published in full. Study B351[48] has been published in abstract form and study B307[28] has yet to be published. Study B351, which was the first phase III trial, did not show any treatment benefit from tegaserod when it was first analysed. In this study a responder had been defined as an individual who obtained complete or considerable relief, for at least 50% of the time at the study endpoint. After completion of the trial it was felt that the definition of response was too stringent and thus the study lacked the necessary sensitivity to detect a treatment difference leading to a type II error. With the agreement of the FDA the definition of response for the subsequent phase III trials B301, B307 and B358 were modified to include subjects whose symptoms were at least somewhat relieved 100% of the time at the study endpoint, as well those achieving at least considerable relief, for at least 50% of the time. Study B351 was retrospectively analysed using these modified criteria, with the revised results showing a 45.7% response rate for tegaserod 6mg twice daily, 38.9% for tegaserod 2mg twice daily, and 33.3% for placebo.[48] This translated in to a treatment benefit over placebo of 12.4% ($p = 0.004$) for the tegaserod 6mg twice daily dose, but no statistically significant benefit from the tegaserod 2mg twice daily dose.

The Asia-Pacific study,[51] which used a different design from the other studies, found a significant therapeutic gain over placebo of 19–24% during the first 4 weeks of treatment, and 13–24% over the full 12 weeks of treatment ($p < 0.01$). Individual symptoms of abdominal pain/discomfort and bloating were also significantly improved.

9.4 Safety

9.4.1 Tolerability and Adverse Events

During the phase III trials regular clinical assessments of patients taking tegaserod were made, including physical examination, pulse, blood pressure, standard laboratory tests and 12-lead ECGs. Given the large numbers of patients included in the available clinical studies, there is now a large amount of safety data available for tegaserod.

In study B301,[49] diarrhoea was the only adverse event to occur significantly more frequently in the tegaserod groups than in the placebo group: occurring in 9.6%, 7.1% and 2.5% of patients using twice daily tegaserod 6mg, 2mg and placebo, respectively. Episodes of diarrhoea were mild and transient, lasting a median of 2 days with the tegaserod 2mg twice daily dose and 4 days with the tegaserod 6mg twice daily dose. After the initial episode, symptoms generally settled and further episodes were rare. Headache was the most frequently reported adverse event, occurring in up to 30.6% of patients using tegaserod, although it also occurred in a similar number of those using placebo. Other symptoms were flu-like illness, which occurred in around 10%, and dizziness in approximately 5%. Nausea, upper respiratory tract infection, back pain and abdominal pain all occurred more frequently in those using placebo than in the tegaserod groups.

Results from study B358[50] also showed that headache was the most frequently reported adverse effect occurring in 9% of treated patients. In order of decreasing frequency other adverse effects were

nausea (approximately 7%), abdominal pain (6%), diarrhoea (6%) and flatulence (6%). Of these, headache, nausea and diarrhoea occurred more frequently in the tegaserod group compared with placebo. Again, episodes of diarrhoea were mild and transient, not leading to dehydration, electrolyte disturbances or hospitalisation.

Serious adverse events were rare in all studies. During the course of study B358, a number of patients underwent abdominal or pelvic surgery, although none of these were felt to be causally related to the medication.[50] Four patients administered tegaserod required cholecystectomies, one an appendicectomy, one a hiatus hernia repair and one a hysterectomy, whilst amongst those taking placebo, one needed a cholecystectomy, two hysterectomies and one surgery for division of adhesions. It is noteworthy that a recent study found that patients with IBS *per se* are at increased risk of abdominal surgery irrespective of treatment.[54] Nonsurgical serious adverse events occurring in the tegaserod group were coronary artery disease, anxiety and a vertebral disc condition, whilst one patient developed seizures during treatment with placebo.[50] There were no serious adverse events during study B301.[49]

No clinically significant changes in heart rate, blood pressure, laboratory parameters or ECGs occurred in either study. During the withdrawal phase of study B358, 13% of patients who had taken tegaserod experienced adverse events compared with 14% in the placebo group, none of these were serious.[50]

Withdrawal from treatment because of adverse events occurred in 5.1% of patients in the tegaserod 6mg twice daily group, 8.7% in the tegaserod 2mg twice daily group and 4.5% in the placebo group in study B301.[49] The drop-out rate due to diarrhoea was 2% in the lower tegaserod dosage group and 2.4% in the higher dosage group. In study B358 similar treatment-related withdrawal rates of 6.8% in the tegaserod group and 4.8% in the placebo group were seen.[50] In the tegaserod group,1.6% of patients discontinued the medication due to diarrhoea. The NNT to experience adverse effects severe enough to lead to discontinuation of the medication was 50, and 62.5 specifically for diarrhoea. The NNT of 7–17 was less than the number-needed-to-harm (NNH) of 50–62.5 suggesting a positive risk-benefit relationship.

In the Asia-Pacific study, the incidence of adverse events was comparable in the tegaserod and placebo groups.[51] The overall discontinuation rate was 16% and 12%, respectively, with those patients withdrawing due to adverse events being 7.7% and 3.1%, and those related specifically to diarrhoea being 2.3% and 0%, respectively. The most frequent adverse event was diarrhoea, which occurred in 10.4% of patients taking tegaserod and 4.2% of those taking placebo. No published data exist relating to adverse events or safety for studies B351 and B307.

One study has specifically addressed the issue of long-term tolerability and safety of tegaserod,[55] and this was one of the largest and longest running clinical trials ever undertaken in patients with IBS. This was an open-label study using a flexible dose-titration protocol, carried out in >500 patients with constipation-predominant IBS over a 12-month period. The dosage of tegaserod was increased from 2mg twice daily to 6mg twice daily if there was an inadequate symptomatic response to therapy, and a reduction in dosage was allowed if there was intolerance; however, once reduced, the dosage of tegaserod could not be increased again. Adverse events were defined as any deterioration in condition from baseline, whether or not this was considered to be related to the use of tegaserod. Events were subdivided into: (i) mild – a symptom that was barely noticeable and did not interfere with functioning; (ii) moderate – a symptom that made the subject uncomfortable or affected performance; and (iii) severe – a severely uncomfortable symptom possibly warranting drug cessation or further treatment. Serious adverse events included those that threatened life or resulted in hospitalisation or disability.

In the majority of patients the dose of tegaserod was increased rapidly culminating in 82% of patients taking the 6mg twice daily dosage by the end of the study.[55] Overall, 53% of patients who re-

ceived tegaserod completed the 12-month treatment period. The most common reason given for withdrawal from the study was treatment ineffectiveness, which occurred in 12% of patients, although 11% withdrew because of adverse events. The remaining patients who withdrew did so for other reasons including withdrawal of consent, a loss to follow-up and protocol violation.

Almost one-quarter of patients had previously received tegaserod. In this group, withdrawals due to adverse effects occurred in a similar proportion to those who were naive to the drug, except for diarrhoea, which was somewhat more common in the previously exposed group (5.1% in previously exposed versus 3.0% in naive). Conversely, withdrawal due to lack of efficacy occurred more frequently in those who were naive to the drug (14.1% naive versus 7.2% previously exposed).[55]

The most frequently occurring adverse events were headache (29.5% all tegaserod-treated patients, 8.3% considered possibly tegaserod related by the investigators) abdominal pain (17.1%, 7.4%), diarrhoea (14.5%, 10.1%), back pain (8.6%, 0.5%) and flatulence (7.6%, 5.5%).[55] Nausea, dyspepsia, flu-like symptoms and insomnia occurred in <10% of all patients and were considered possibly related to therapy in <3%. Severe adverse events including abdominal pain, headache, diarrhoea, constipation and flatulence were seen in 14.3% of patients, 4.4% experienced serious adverse events, and 1.7% of patients in the study experienced more than one serious adverse event. One patient had a 2-day episode of severe abdominal pain after 28 weeks of treatment, which was considered to be possibly related to treatment; however, the patient continued taking the medication and completed the study. Other serious adverse reactions were considered unlikely to be related to drug therapy, these included abdominal pain in four patients, chest pain and gall stones in two patients each, back pain, constipation, cystadenofibroma, depression, an ovarian cyst and pelvic adhesions in one patient each.

Of the 11.2% of patients who discontinued treatment, the most common reason given was (in order of decreasing frequency) diarrhoea (3.5%), abdominal pain (2.8%) flatulence (2.6%), headache (1.1%), nausea (0.9%), constipation (0.5%), alopecia (0.4%), back pain (0.4%), dizziness (0.4%) and dyspepsia (0.4%). The drop-out rate from the study was moderately high; however, this is not surprising given the length of the study and the multiple visits that were required. In addition, considering the relapsing-remitting course of IBS, some patients are likely to have withdrawn from the study during the 12-month period because they became free from symptoms. The drop-out rate of 15% in the first 3 months of the study is comparable to other trials;[56,57] however, there are no data to compare drop-out rates in an IBS study of this duration. No clinically relevant abnormalities were detected in repeated laboratory parameters, except for one patient who was withdrawn following the worsening of a pre-existing eosinophilia, possibly related to drug allergy. There were minor upward and downward fluctuations in blood pressure recordings during the study, with only one thought to be of clinical significance, although judged to be unrelated to drug therapy by the investigators. There were no clinically significant changes in heart rate or bodyweight during the study. All ECG recordings showed no significant abnormalities and in particular there were no changes in the QTc intervals.

Another recently published study was specifically designed to assess the safety and tolerability of tegaserod in the subgroup of IBS patients with diarrhoea.[32] Eighty-six male and female patients who had IBS and diarrhoea for >25% of the time were randomised to receive twice-daily tegaserod 6mg and 2mg, or placebo for 8 weeks, following a 2-week baseline period. The results of this study demonstrated that overall adverse events were not significantly more common in the tegaserod groups compared with placebo. Adverse events which occurred with a frequency of >10% were diarrhoea, abdominal pain, headache, flatulence and fatigue. The frequency of diarrhoea was 18%, 49% and 35% with twice-daily tegaserod 6mg, 2mg and placebo, respectively. When data from both the tegaserod groups were pooled, the diarrhoea rates for active treatment and placebo were similar at 33% and 35%.

No complications such as dehydration or electrolyte disturbances occurred. Nineteen patients, all in the tegaserod groups, withdrew from the study, 11 of these due to adverse effects. Five patients withdrew due to diarrhoea or abdominal pain, the others withdrew as a consequence of adverse effects which did not occur in more than one patient, except headache. No serious adverse events were reported.

9.4.2 Cardiac Safety Profile of Tegaserod

There is a well documented tendency for some gastrointestinal prokinetic drugs to cause prolongation of the QTc interval and thus predispose to ventricular arrhythmias, a problem which led to the withdrawal of cisapride. This effect is thought to be due to blockade of the rapid component of the delayed potassium rectifier channel in cardiac ventricular myocytes, which is a major potassium outflow current from the heart, and is partly responsible for termination of the action potential during the plateau phase. Blockade of the channel therefore results in delayed cardiac repolarisation and the possible development of arrhythmias.

Early preclinical studies suggested that tegaserod is devoid of cardiac effects when used in therapeutic dosages. Subsequently, >10 000 ECG recordings have been analysed in humans administered tegaserod,[31] over 2500 of these in patients with IBS[58] some of whom were known to have cardiac disease or were co-administered drugs (such as antidepressants or antihistamines) that could prolong the QTc interval. Analysis of these ECGs showed that heart rate, PR, QRS and QTc intervals were not significantly different between tegaserod and placebo recipients. Furthermore there was no dose-response relationship relating to ECG parameters, and no effect was seen in the elderly.[58] In addition, tegaserod has been used without ill-effect in a small number of patients exhibiting prolongation of the QTc interval at baseline.[58] The most frequently occurring ECG changes in patients given tegaserod were nonspecific ST changes, T wave abnormalities and first degree atrioventricular block but they are unlikely to be of any clinical significance because they occurred with similar frequency in placebo recipients.[58]

10. Systematic Reviews and Meta-Analyses of Tegaserod

Two systematic reviews[47,59] and one meta-analysis[60] pooling data from randomised controlled trials evaluating tegaserod in patients with IBS have been published. The first systematic review by Jones et al.[59] assessed six studies, including three fully published papers B301,[49] B358[50] and B357[61] and three abstracts B251,[45] B202[46] and B351.[48] B357 was a small pharmacodynamic study showing that tegaserod accelerated orocaecal transit in humans compared with placebo.[61] The second systematic review was undertaken as part of a broader review of the treatment of IBS in North America.[47] This study included four trials: three published trials (B301,[49] B358[50] and the Asia-Pacific study[51]) and another study which remains in abstract form[62] and was not included in the review by Jones et al. Both reviews concluded that there was a positive effect with tegaserod of approximately 5–20% over placebo. Subgroup analysis revealed less bloating, less abdominal discomfort, and improved bowel satisfaction compared with placebo. Diarrhoea was the most frequently reported adverse effect, occurring in approximately 10% of patients using tegaserod and leading to a drop-out rate of 1–2%. In comparison, diarrhoea occurred in around 5% of those using placebo. There were no differences in occurrences of abdominal/pelvic surgery between the two groups. Male patients comprised <20% of the total study population and although there was a non-significant trend towards global symptom improvement in this group, the numbers were considered too small to exclude a type II error.

One meta-analysis has been performed and published in abstract form.[60] This included >4000 patients from unspecified phase III placebo-controlled trials. The combined results suggested that tegaserod 6mg twice daily achieved global symptom relief significantly more frequently than placebo with a relative risk (RR) of 1.16 (95% CI: 1.07–1.26) and a NNT of 10. There were no significant differences in the total number of adverse effects, or in the incidence of abdominal or pelvic surgeries between tegaserod and placebo recipients; however, diar-

rhoea was more common in patients using tegaserod (RR = 2.15 [95% CI: 1.65–2.80]; NNH = 50).

11. Conclusion

Tegaserod is an effective therapy for the multiple symptoms of IBS in females with constipation-predominant disease. The optimal dosage appears to be 6mg twice daily. Treatment benefit over placebo is approximately 5–20%, with a NNT of between 5–15. The overall response rate is likely to be in the region of 50%. Efficacy in men is currently uncertain.

Tegaserod was well tolerated in clinical trials of up to 12 months duration. Diarrhoea was the most common adverse effect affecting 5–10% of patients; however, it was often transient and self limited, leading to treatment discontinuation in 1–2% of patients. Other adverse effects included headache and nausea, although these did not occur consistently more frequently in patients taking tegaserod compared with those taking placebo. Approximately 7% of patients using tegaserod could not tolerate the drug because of to adverse effects. The NNH was approximately 50–60. There is now good evidence to suggest that that tegaserod does not affect the ECG and is devoid of cardiotoxicity. The incidences of abdominal and pelvic surgeries were not more frequent in tegaserod-treated patients compared with those using placebo.

Inappropriate prescription of the 5-HT_3 antagonist group of drugs such as alosetron to the wrong subgroup of patients with IBS is associated with potentially serious consequences. In contrast, although tegaserod is only indicated for constipation-predominant IBS, administration to other subgroups is unlikely to cause major problems.

Acknowledgements

Dr Whorwell has acted as an advisor to a number of pharmaceutical companies including Novartis for which he has received remuneration. Dr Lea is currently in receipt of an educational grant from Novartis Pharmaceuticals.

References

1. Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. Gastroenterology 1991; 100 (4): 998-1005
2. Switz DM. What the gastroenterologist does all day: a survey of a state society's practice. Gastroenterology 1976; 70 (6): 1048-50
3. Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. Gastroenterology 2002; 123 (6): 2108-31
4. Drossman DA, Li Z, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders: prevalence, sociodemography, and health impact. Dig Dis Sci 1993; 38 (9): 1569-80
5. Manning AP, Thompson WG, Heaton KW, et al. Towards positive diagnosis of the irritable bowel. BMJ 1978; 2 (6138): 653-4
6. Thompson WG, Creed FH, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. Gastroenterol Int 1992; 5: 75-91
7. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. Gut 1999; 45 Suppl. 2: II43-7
8. Olden KW. Diagnosis of irritable bowel syndrome. Gastroenterology 2002; 122 (6): 1701-14
9. Talley NJ, Zinsmeister AR, Melton III LJ. Irritable bowel syndrome in a community: symptom subgroups, risk factors, and health care utilization. Am J Epidemiol 1995; 142 (1): 76-83
10. Hahn B, Watson M, Yan S, et al. Irritable bowel syndrome symptom patterns: frequency, duration, and severity. Dig Dis Sci 1998; 43 (12): 2715-8
11. Lea R, Whorwell PJ. Quality of life in irritable bowel syndrome. Pharmacoeconomics 2001; 19 (6): 643-53
12. Kim DY, Camilleri M. Serotonin: a mediator of the brain-gut connection. Am J Gastroenterol 2000; 95 (10): 2698-709
13. Talley NJ. Serotoninergic neuroenteric modulators. Lancet 2001; 358 (9298): 2061-8
14. Bach T, Syversveen T, Kvingedal AM, et al. 5-HT4(a) and 5-HT4(b) receptors have nearly identical pharmacology and are both expressed in human atrium and ventricle. Naunyn Schmiedebergs Arch Pharmacol 2001; 363 (2): 146-60
15. Corsetti M, Tack J. Tegaserod: a new 5-HT4 agonist in the treatment of irritable bowel syndrome. Expert Opin Pharmacother 2002; 3: 1211-8
16. Tonini M, Messori E, Franceschetti GP, et al. Characterization of the 5-HT receptor potentiating neuromuscular cholinergic transmission in strips of human isolated detrusor muscle. Br J Pharmacol 1994; 113 (1): 1-2
17. Pata C, Erdal ME, Derici E, et al. Serotonin transporter gene polymorphism in irritable bowel syndrome. Am J Gastroenterol 2002; 97 (7): 1780-4
18. Camilleri M, Atanasova E, Carlson PJ, et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. Gastroenterology 2002; 123 (2): 425-32
19. Klein KB. Controlled treatment trials in the irritable bowel syndrome: a critique. Gastroenterology 1988; 95 (1): 232-41
20. Northcutt A, Mangel AW, Hamm LR, et al. Persistent placebo response during a year long controlled trial of IBS treatment [abstract no. 3243]. Gastroenterology 2001; 120 (5) Suppl. 1: A640

21. Spiller RC. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. Am J Med 1999; 107 (5A): 91S-7S
22. Veldhuyzen van Zanten SJ, Talley NJ, Bytzer P, et al. Design of treatment trials for functional gastrointestinal disorders. Gut 1999; 45 Suppl. 2: II69-77
23. Talley NJ. Review article: 5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implications. Aliment Pharmacol Ther 1992; 6 (3): 273-89
24. Kamm MA. Review article: the complexity of drug development for irritable bowel syndrome. Aliment Pharmacol Ther 2002; 16 (3): 343-51
25. Bearcroft CP, Andre EA, Farthing MJ. In vivo effects of the 5-HT3 antagonist alosetron on basal and cholera toxin-induced secretion in the human jejunum: a segmental perfusion study. Aliment Pharmacol Ther 1997; 11 (6): 1109-14
26. Houghton LA, Foster JM, Whorwell PJ. Alosetron, a 5-HT3 receptor antagonist, delays colonic transit in patients with irritable bowel syndrome and healthy volunteers. Aliment Pharmacol Ther 2000; 14 (6): 775-82
27. Kozlowski CM, Green A, Grundy D, et al. The 5-HT(3) receptor antagonist alosetron inhibits the colorectal distension induced depressor response and spinal c-fos expression in the anaesthetised rat. Gut 2000; 46 (4): 474-80
28. Novartis Pharmaceuticals, 2002 (Data on file)
29. Pfannkuche H, Bhul T, Gamse R, et al. The properties of a new prokinetically active drug SDZ HTF919. Neurogastroenterol Motil 1995; 7
30. Clark RB, Knoll BJ, Barber R. Partial agonists and G protein-coupled receptor desensitization. Trends Pharmacol Sci 1999; 20 (7): 279-86
31. Camilleri M. Review article: tegaserod. Aliment Pharmacol Ther 2001; 15 (3): 277-89
32. Fidelholtz J, Smith W, Rawls J, et al. Safety and tolerability of tegaserod in patients with irritable bowel syndrome and diarrhea symptoms. Am J Gastroenterol 2002; 97 (5): 1176-81
33. Grider JR, Foxx-Orenstein AE, Jin JG. 5-Hydroxytryptamine4 receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. Gastroenterology 1998; 115 (2): 370-80
34. Stoner M, Arcuni J, Lee J, et al. A selective 5-HT4 receptor agonist induces cAMP mediated Cl- efflux from rat colonocytes [abstract no. G2827]. Gastroenterology 1999 Apr; 116 (4) Pt 2: A648
35. Fioramonti J, Million M, Bueno L. Investigations on a 5-HT4 agonist (SDZ HTF919) and its main metabolite in conscious dogs: effects on gastrointestinal motility and impaired gastric emptying [abstract no. G3103]. Gastroenterology 1998 Apr; 114 (4) Pt 2: A752
36. Schikowski A, Thewissen M, Mathis C, et al. Serotonin type-4 receptors modulate the sensitivity of intramural mechanoreceptive afferents of the cat rectum. Neurogastroenterol Motil 2002; 14 (3): 221-7
37. Coffin B, Farmachidi JP, Rueegg P, et al. Tegaserod, a 5-HT4 receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects. Aliment Pharmacol Ther 2003; 17 (4): 577-85
38. Drici MD, Ebert SN, Wang WX, et al. Comparison of tegaserod (HTF 919) and its main human metabolite with cisapride and erythromycin on cardiac repolarization in the isolated rabbit heart. J Cardiovasc Pharmacol 1999; 34 (1): 82-8
39. Appel-Dingemanse S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT(4) receptor partial agonist with promotile activity. Clin Pharmacokinet 2002; 41 (13): 1021-42
40. Appel-Dingemanse S, Hirschberg Y, Osborne S, et al. Multiple-dose pharmacokinetics confirm no accumulation and dose proportionality of the novel promotile drug tegaserod (HTF 919). Eur J Clin Pharmacol 2001; 56 (12): 889-91
41. Ledford P, On N, Ligueros-Saylan M, et al. Tegaserod does not significantly affect the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects [abstract no. 5445]. Gastroenterology 2000; 118 (4) Suppl. 2
42. Zhou H, Walter Y, Hubert M, et al. Tegaserod (HTF919) does not decrease the effectiveness of an oral contraceptive when co-administered to healthy female subjects [abstract no. 1024]. Gastroenterology 2000; 118 (4) Suppl. 2
43. Zhou H, Horowitz A, Ledford PC, et al. The effects of tegaserod (HTF 919) on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects. J Clin Pharmacol 2001; 41 (10): 1131-9
44. Zhou H, Khalilieh S, Svendsen K, et al. Tegaserod coadministration does not alter the pharmacokinetics of theophylline in healthy subjects. J Clin Pharmacol 2001; 41 (9): 987-93
45. Lefkowitz M, Ruegg P, Shi Y, et al. Relief of overall GI symptoms and abdominal pain and discomfort as outcome measures in a clinical trial of irritable bowel syndrome with HTF919 [abstract no. G4462]. Gastroenterology 1999 Apr; 116 (4) Pt 2: A1027
46. Hamiling J, Bang C, Tarpila S. Titration regimen indicates partial 5-HT4 agonist HFT919 improves symptoms of constipation predominant irritable bowel syndrome (C-IBS). Digestion 1998; 59 Suppl. 3: 735
47. Brandt LJ, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol 2002; 97 (11 Suppl.): S7-26
48. Lefkowitz M, Shi Y, Schmitt C, et al. The 5HT4 partial agonist, tegaserod, improves abdominal discomfort/pain and normalises altered bowel function in irritable bowel syndrome. Am J Gastroenterol 1999; 94: 2676
49. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001; 15 (10): 1655-66
50. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002; 16 (11): 1877-88
51. Kellow J, Lee O, Chang F, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003; 52 (5): 671-6
52. Hawkey CJ. Irritable bowel syndrome clinical trial design: future needs. Am J Med 1999; 107 (5A): 98S-102S
53. Lefkowitz M, Ruegg P, Shi Y, et al. Validation of a global relief measure in two clinical trials of irritable bowel syndrome with tegaserod. Digestion 1998; 59: 735
54. Hasler WL, Schoenfeld P. Systematic review: abdominal and pelvic surgery in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2003; 17 (8): 997-1005
55. Tougas G, Snape Jr WJ, Otten MH, et al. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2002; 16 (10): 1701-8

56. Dobrilla G, Imbimbo BP, Piazzi L, et al. Long-term treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo controlled clinical trial. Gut 1990; 31 (3): 355-8
57. Gilbody JS, Fletcher CP, Hughes IW, et al. Comparison of two different formulations of mebeverine hydrochloride in irritable bowel syndrome. Int J Clin Pract 2000; 54 (7): 461-4
58. Morganroth J, Ruegg PC, Dunger-Baldauf C, et al. Tegaserod, a 5-hydroxytryptamine type 4 receptor partial agonist, is devoid of electrocardiographic effects. Am J Gastroenterol 2002; 97 (9): 2321-7
59. Jones BW, Moore DJ, Robinson SM, et al. A systematic review of tegaserod for the treatment of irritable bowel syndrome. J Clin Pharm Ther 2002; 27 (5): 343-52
60. Schoenfeld P, Chey W, Drossman DA, et al. Effectiveness and safety of tegaserod in the treatment of irritable bowel syndrome: a meta-analysis of randomised controlled trials [abstract no. T1486]. Gastroenterology 2002 Apr; 122 (4): A465
61. Prather CM, Camilleri M, Zinsmeister AR, et al. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000; 118 (3): 463-8
62. Whorwell PJ, Krumbolz S, Muller-Lissner SA, et al. Tegaserod has a favourable safety and tolerability profile in patients with constipation predominant and alternating forms of irritable bowel syndrome. Gastroenterology 2000, 118

Correspondence and offprints: Dr *Peter J. Whorwell*, Medical Academic Department, Education and Research Centre, South Manchester University Hospitals, Wythenshawe, Manchester, M23 2LT, UK.
E-mail: peter.whorwell@smuht.nwest.nhs.uk