Aliment Pharmacol Ther 2002; 16: 1701–1708. doi:10.1046/j.0269-2813.2002.01347.x

Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome

G. TOUGAS*, W. J. SNAPE JR†, M. H. OTTEN‡, D. L. EARNEST§, K. -E. LANGAKER¶, R. E. PRUITT**, E. PECHER††, B. NAULT†† & M. A. ROJAVIN§

**Medicine and Gastroenterology, McMaster University Medical Centre, Hamilton, Canada; †Medical Center, Long Beach, CA, USA; ‡Hospital Eemland, Amersfoort, The Netherlands; §Novartis Pharmaceuticals, East Hanover, NJ, USA; ¶Medical Clinic, Oslo, Norway; **St Thomas Medical Plaza West, Nashville, TN, USA; ††Novartis Pharma AG, Basel, Switzerland*

Accepted for publication 3 July 2002

SUMMARY

Background: Tegaserod is a 5-hydroxytryptamine-4 receptor partial agonist. Oral administration causes gastrointestinal effects resulting in increased gastrointestinal motility and attenuation of visceral sensation.

Aim: To determine the long-term safety and tolerability of tegaserod in patients suffering from irritable bowel syndrome with constipation as the predominant symptom of altered bowel habits.

Method: A multicentre, open-label study with flexible dose titration of tegaserod in out-patients suffering from constipation-predominant irritable bowel syndrome.

Results: A total of 579 patients with constipation-predominant irritable bowel syndrome were treated with tegaserod. Of these, 304 (53%) completed the trial. The most common adverse events, classified as related to tegaserod for any dose, were mild and transient diarrhoea (10.1%), headache (8.3%), abdominal pain (7.4%) and flatulence (5.5%). Forty serious adverse events were reported in 25 patients (4.4% of patients) leading to discontinuation in six patients. There was one serious adverse event, acute abdominal pain, classified as possibly related to tegaserod. There were no consistent differences in adverse events between patients previously exposed to tegaserod and those treated *de novo*. No pattern-forming tegaserod-related abnormalities in haematological and biochemical laboratory tests, urinalysis, blood pressure, pulse rate or electrocardiograms were found.

Conclusions: Tegaserod appears to be well tolerated in the treatment of patients with constipation-predominant irritable bowel syndrome. The adverse event profile, clinical laboratory evaluations, vital signs and electrocardiogram recordings revealed no evidence of any unexpected adverse events, and suggest that treatment is safe over a 12-month period.

INTRODUCTION

Irritable bowel syndrome is a common, chronic, functional gastrointestinal disorder. Its symptoms range from mild abdominal discomfort to severe and intractable abdominal pain and symptoms of bowel dysfunction, which exert profound effects on a person's quality of life. The condition is formally characterized by chronic recurrent abdominal pain associated with defecation, or a change in bowel habit with disordered defecation and abdominal distension.[1–3] The aetiology of irritable bowel syndrome is poorly understood, but is probably multifactorial, with alterations in gastrointestinal motility, visceral perception and psychosocial

Correspondence to: Dr M. A. Rojavin, Novartis Pharmaceuticals, One Health Plaza, East Hanover, NJ 07936, USA.
E-mail: Mikhail.rojavin@pharma.novartis.com

factors all contributing to the overall spectrum of symptoms.[1, 3, 4] On the basis of their predominant symptom, patients can be classified into three groups: diarrhoea-predominant irritable bowel syndrome, constipation-predominant irritable bowel syndrome or irritable bowel syndrome with alternating bowel movement. Until recently, there was no specific therapy available for the treatment of irritable bowel syndrome and physicians relied on the empirical treatment of specific individual symptoms of the disorder.

Tegaserod, an aminoguanidine-indole compound, is a selective partial agonist of 5-hydroxytryptamine-4 receptors. Activation of these receptors in the gastrointestinal tract triggers the peristaltic reflex and motor activity.[5, 6] Recent evidence suggests that 5-hydroxytryptamine-4 receptors may play a role in the modulation of visceral sensitivity and, accordingly, the potential exists for a beneficial effect of tegaserod in altered visceral perception.[7] Clinical studies have shown that tegaserod is effective in the therapy of patients with constipation-predominant irritable bowel syndrome, producing a normalization of bowel habits and relieving abdominal discomfort/pain and bloating.[8, 9]

The primary objective of the current investigation was to determine the safety and tolerability of long-term therapy with tegaserod in the treatment of patients suffering from constipation-predominant irritable bowel syndrome. The efficacy of long-term tegaserod therapy in the treatment of constipation-predominant irritable bowel syndrome was also evaluated by the subject's global assessment of changes in the severity of gastrointestinal symptoms. The observed efficacy suggested a beneficial response to tegaserod treatment sustained for at least 1 year. However, as the study was not placebo-controlled, and the placebo effect in irritable bowel syndrome patients can be high and long-lasting,[10] efficacy results will not be presented in this paper.

PATIENTS AND METHODS

Study population

The study population included male and non-pregnant female out-patients, aged 18–70 years, suffering from constipation-predominant irritable bowel syndrome as defined by the Rome 1 criteria[11] and by the responses to a questionnaire adapted from Drossman *et al.*[12, 13] Females of childbearing potential had to practice an approved method of contraception and agree to continue doing so throughout the study period. All patients had undergone appropriate endoscopic or radiological examination to exclude other causes of gastrointestinal symptoms and dysfunction, and all provided written informed consent to participate in the study.

Patients were excluded if they had clinically relevant diarrhoea as a component of the disorder or if they suffered from other conditions which could affect gastrointestinal motility. Patients were also excluded if they had clinical evidence of significant cardiovascular, respiratory, renal, hepatic, haematological, neurological, or any other disease which may have interfered with the successful completion of the study, or if they were taking concomitant medications prohibited by the protocol (including certain anti-arrhythmics, narcotics and prokinetic agents).

Medication

In this open-label study, tegaserod was administered at a dosage of 2 mg b.d. or 6 mg b.d. during the 12-month active treatment period. One tablet was taken with water 30–60 min before meals in the morning and in the evening. During the first month, patients received 4 mg daily, and then either 4 mg or 12 mg daily during the following months depending upon the therapeutic effect assessed during the visits at months 1, 2, 4, 6, 8 and 10. A dose reduction from 12 mg to 4 mg daily was allowed if the drug was poorly tolerated, but, once reduced, a subsequent dose increase from 4 mg back up to 12 mg daily was not permitted.

Rescue medication for the relief of severe, symptomatic constipation was allowed and consisted of magnesium sulphate, lactulose, sodium sulphate, sodium picosulfate, polyethylene glycol or bisacodyl suppository. Patients who received inadequate relief overnight could use other forms of laxatives (including enemas). Patients using chronic stable doses of bulking agents (e.g. psyllium seed extracts) could continue to use the agent at the same dose throughout the study. The use of anti-diarrhoeal medication, such as loperamide, was allowed.

Visit schedule and assessments

The visit schedule for patients was designed as follows. Upon signing the informed consent, patients underwent physical examination, laboratory tests and other

procedures in order to evaluate whether they satisfied the inclusion/exclusion criteria. After completion of the 1-week screening period, qualifying patients were randomized into the study. They were further monitored (vital signs and physical examination, laboratory tests, pregnancy screening and assessment of their gastrointestinal symptoms) during office visits at months 1, 2, 4, 6, 8, 10 and 12. An electrocardiogram was recorded during the screening period and then repeated at months 2, 6 and 12 of the study. Telephone monitoring was conducted between the office visits at months 3, 5, 7, 9 and 11 by collecting information about gastrointestinal-related symptoms and recording patients' comments.

Safety assessments

Safety assessments involved the recording of all adverse events, with their severity and relationship to the study drug and influence on the course of the study, regular monitoring of haematology, blood chemistry and urinalysis, repeated pregnancy testing, regular recordings of vital signs and electrocardiograms and the performance of physical examinations. Electrocardiograms from all the sites were interpreted centrally by an independent expert.

An adverse event was defined as any adverse change from the baseline condition which occurred during the course of treatment, whether considered to be related to the study medication or not. All adverse events were further subdivided into mild (a symptom barely noticeable to a subject; does not influence performance or functioning), moderate (symptom of sufficient severity to make subject uncomfortable; performance of daily activities influenced) and severe. A severe adverse event caused severe discomfort, possibly resulting in the cessation of test drug therapy and requiring treatment for the symptom.

A serious adverse event was any event which was fatal or considered to be life-threatening, required or prolonged hospitalization, caused permanent disability, led to cancer or congenital anomaly or resulted from study drug overdose.

Essentially all safety events which the investigators classified as serious were reported as such, even if the event did not strictly fulfil the above criteria.

The haematology, biochemistry, urinalysis and pregnancy screening tests were performed by a central laboratory.

Efficacy assessments

Efficacy was assessed in this clinical trial by recording the subject's global assessment of gastrointestinal symptoms. Efficacy results are not given in this paper.

Statistical analyses

Data were collected from at least 300 patients during 1 year of treatment. Additional patients were enrolled to compensate for dropouts. The main focus of this trial was to obtain long-term safety information. Safety analyses included summaries of the incidence of treatment-emergent adverse events, vital signs, laboratory data and electrocardiogram data.

RESULTS

Recruited and treated patients

A total of 601 patients were enrolled at 35 centres in Canada, Finland, France, Germany, Italy, Netherlands, Norway, UK and the USA. A total of 579 patients entered the treatment phase of the study. The efficacy and safety populations consisted of 567 patients (97.9% of those who entered the treatment phase). Twelve patients were excluded from the efficacy and safety evaluation due to a lack of post-baseline assessment. A total of 138 (24%) of the patients had received tegaserod in previous trials. Withdrawals due to adverse events occurred in a similar proportion in patients who had previously received tegaserod and in those who were receiving the drug for the first time. Discontinuations due to a lack of efficacy were more common in the latter group: 10 patients (7.2%) vs. 62 patients (14.1%). Figure 1 summarizes the ultimate disposition of all the patients screened for recruitment into the study.

Overall, 52.5% of the patients who received treatment with the study drug completed the planned 12-month treatment period.

Table 1 provides details of the background and demographic data of the patients on entry into the study.

Consistent with statistical data on long-standing irritable bowel syndrome,[14] as well as with other studies of tegaserod in irritable bowel syndrome patients,[5] the study population was predominantly composed of middle-aged, female Caucasians who had a history of chronic constipation-predominant irritable bowel syndrome.

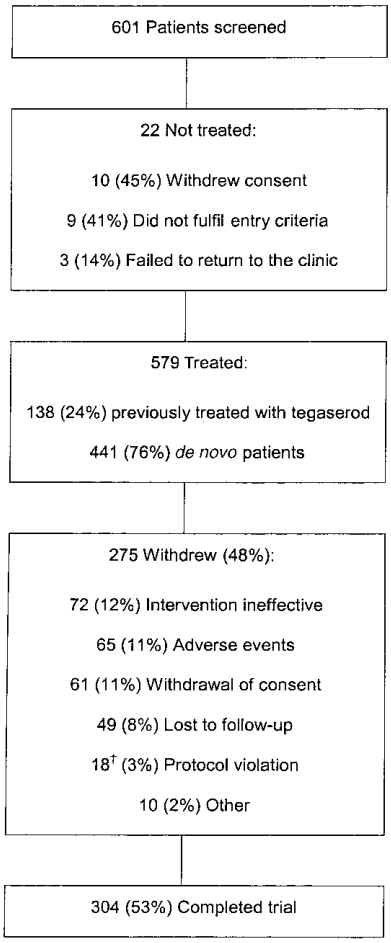

Figure 1. The study flow chart. † Includes 7 patients who discontinued owing to pregnancy.

Table 1. Demographic and baseline characteristics of the study population

Parameter	All treated patients ($n = 579$)
Sex, *n* (%)	
Male	56 (9.7)
Female	523 (90.3)
Age (years) (mean ± s.d.)	44.2 ± 12.4
Race, *n* (%)	
Caucasian	538 (92.9)
Black	33 (5.7)
Asian/Oriental	4 (0.7)
Others	4 (0.7)
Weight (kg) (mean ± s.d.)	68.6 ± 14.5
Median duration of symptoms (years)	6.4
Previously treated, *n* (%)	138 (23.8)

Dosage and patient exposure

In the majority of patients, the dose of tegaserod was increased to 12 mg daily within the first 3 months of therapy. Down-titrations were infrequent so that, at the end of the 12-month study period, 82% of the patients were receiving 12 mg of tegaserod daily. Patients were exposed to tegaserod, 12 mg/day, for a mean duration of 209.7 ± 122.01 days (mean ± s.d.).

Safety

The most commonly reported adverse events during the course of the investigation are summarized in Table 2. Overall, the majority of adverse events were gastrointestinal disturbances, which affected 46% of the population. The most common tegaserod-related adverse events were mild and transient diarrhoea (10.1%), headache (8.3%), abdominal pain (7.4%) and flatulence (5.5%). When analysed separately for patients previously exposed to tegaserod and those treated *de novo*, the above-mentioned adverse events were distributed almost equally, with abdominal pain registered somewhat more frequently in tegaserod-naive patients (8.1% vs. 5.1%). Nausea, dyspepsia and insomnia related to tegaserod were equally reported by 1–3% of patients.

A total of 81 (14.3%) patients had severe adverse events, among which the most common were abdominal pain, headache, diarrhoea, constipation and flatulence.

No deaths occurred during the course of the study. During the 12-month treatment period, 25 patients (4.4%) experienced a total of 40 serious adverse events. One 2-day episode of severe abdominal pain, reported after 199 days of therapy with tegaserod 12 mg daily, was considered to be possibly drug related. However, the patient continued to participate in the study and subsequently completed the full course of treatment. Ten patients experienced more than one serious adverse event during the course of the study. All remaining serious adverse events were considered by investigators as either unlikely to be related or not related to treatment with the study drug. They included abdominal pain in four patients (0.7%), chest pain and cholelithiasis in two patients (0.4%) each, and back pain, constipation, cystadenofibroma, depression, ovarian cyst and pelvic adhesion in one patient (0.2%) each.

A total of 65 patients (11.2% of all patients, or 23.6% of discontinued patients) terminated study participation due to adverse events, six for serious adverse events.

Table 2. Most commonly reported adverse events

Adverse event	*n* (%)* all tegaserod-treated patients			*n* (%)* possibly related to tegaserod†		
	All ($n = 567$)	Previous tegaserod exposure ($n = 137$)	No previous tegaserod exposure ($n = 430$)	All ($n = 567$)	Previous tegaserod exposure ($n = 137$)	No previous tegaserod exposure ($n = 430$)
Abdominal pain	97 (17.1)	19 (13.9)	78 (18.1)	42 (7.4)	7 (5.1)	35 (8.1)
Back pain	49 (8.6)	15 (11.0)	34 (7.9)	3 (0.5)	1 (0.7)	2 (0.5)
Diarrhoea	83 (14.6)	21 (15.3)	62 (14.4)	57 (10.1)	17 (12.4)	40 (9.3)
Dyspepsia	41 (7.2)	9 (6.6)	32 (7.4)	12 (2.1)	4 (2.9)	8 (1.9)
Flatulence	43 (7.6)	9 (6.6)	34 (7.9)	31 (5.5)	7 (5.1)	24 (5.6)
Headache	167 (29.5)	35 (25.6)	132 (30.7)	47 (8.3)	8 (5.8)	39 (9.1)
Influenza-like symptoms	34 (6.0)	6 (4.4)	28 (6.5)	1 (0.2)	0 (0.0)	1 (0.2)
Insomnia	29 (5.1)	5 (3.7)	24 (5.6)	8 (1.4)	0 (0.0)	8 (1.9)
Nausea	46 (8.1)	10 (7.3)	36 (8.4)	19 (3.4)	5 (3.7)	14 (3.3)
Pharyngitis	30 (5.3)	7 (5.1)	23 (5.4)	1 (0.2)	0 (0.0)	1 (0.2)
Rhinitis	39 (6.9)	14 (10.2)	25 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	47 (8.3)	13 (9.5)	34 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	92 (16.2)	18 (13.1)	74 (17.2)	3 (0.5)	0 (0.0)	3 (0.7)

* Events with frequency > 5% for any of the groups.
† Events included were, in the opinion of the investigator, possibly, probably or definitely related to tegaserod use.

Table 3. Adverse events leading to premature discontinuation of tegaserod therapy

Adverse event	*n* (%) all tegaserod-treated patients*		
	All patients ($n = 567$)	Previous tegaserod exposure ($n = 137$)	No previous tegaserod exposure ($n = 430$)
Diarrhoea	20 (3.5)	7 (5.1)	13 (3.0)
Abdominal pain	16 (2.8)	3 (2.2)	13 (3.0)
Flatulence	15 (2.6)	3 (2.2)	12 (2.8)
Headache	6 (1.1)	0 (0.0)	6 (1.4)
Nausea	5 (0.9)	1 (0.7)	4 (0.9)
Constipation	3 (0.5)	0 (0.0)	3 (0.7)
Alopecia	2 (0.4)	0 (0.0)	2 (0.5)
Back pain	2 (0.4)	1 (0.7)	1 (0.2)
Dizziness	2 (0.4)	0 (0.0)	2 (0.5)
Dyspepsia	2 (0.4)	1 (0.7)	1 (0.2)

* Events displayed by frequency with incidence in two or more patients in the first column.

Table 3 summarizes the adverse events which led to the premature discontinuation of treatment with the study medication in at least one patient in either dose level group.

Adverse events affecting the gastrointestinal system were those which most commonly led to the premature discontinuation of therapy. Relatively few patients discontinued therapy for any specific adverse event, with discontinuations due to diarrhoea (3.5%) being the most common reason. However, these cases were not accompanied by dehydration or electrolyte imbalance, and did not require hospitalization. There was practically no imbalance in gastrointestinal-related adverse events causing discontinuation between subjects previously exposed to tegaserod and newly treated patients, except for diarrhoea, which was somewhat more frequent in the former group (5.1% vs. 3.0%).

Other reasons for patient discontinuation from the study are presented in Table 4. They include a lack of efficacy, withdrawal of consent, failure to return to the clinical office for continued participation, etc. *De novo*-treated patients were discontinued from the study more

Table 4. Reasons for discontinuation from the study

Reason for discontinuation	All patients entering the study treatment phase, *n* (%)	Previous tegaserod exposure, *n* (%)	No previous tegaserod exposure, *n* (%)
Total patients discontinued	275 (100.0)	51 (100.0)	224 (100.0)
Lack of efficacy	72 (26.2)	10 (19.6)	62 (27.7)
Adverse event	65 (23.6)	11 (21.6)	54 (24.1)
Withdrawal of consent	61 (22.2)	17 (33.3)	44 (19.6)
Failed to return	49 (17.8)	9 (17.6)	40 (17.9)
Protocol violation	18 (6.5)	0 (0.0)	18 (8.0)
Other	10 (3.6)	4 (7.8)	6 (2.7)

frequently due to a lack of efficacy (27.7% vs. 19.6%) and protocol violations (8.0% vs. 0.0%), mostly for the use of exclusionary concomitant medications, as compared to patients previously treated with tegaserod. The latter group had more discontinuations due to withdrawal of consent (33.3% vs. 19.6%).

In the patient population of the study, repeated laboratory evaluations made during the course of the 12-month period of therapy showed a number of abnormalities which could be classified as clinically notable. In general, such abnormalities were isolated fluctuations which were asymptomatic and which were unconfirmed at later evaluations. In some cases, they reflected the presence of other medical conditions, such as diabetes mellitus, which were present before entry into the trial and which remained stable during the study period. One patient was prematurely withdrawn on day 40 of the study during treatment with tegaserod 12 mg daily because of worsening of a pre-existing eosinophilia which was considered to be possible evidence of an allergy. The results of the other laboratory evaluations of blood and urine performed during the course of the study were generally unremarkable and failed to reveal any specific pattern of abnormalities during prolonged administration of the study drug.

Blood pressure/pulse data revealed a small number of patients in whom blood pressure fell within clinically notable ranges (for systolic blood pressure, either ≤ 90 + decrease ≥ 20 or < 75 mmHg; for diastolic blood pressure, either ≤ 50 + decrease ≥ 15 or < 40 mmHg). Treatment-emergent, lowered, sitting systolic and diastolic blood pressure was registered in 10 (1.8%) and seven (1.2%) patients, respectively. However, with the exception of patients in whom blood pressure elevations were considered to represent previously undiagnosed essential hypertension and one known hypertensive patient who experienced an episode of severe hypertension reported as a serious adverse event (considered to be unrelated to therapy), none of the blood pressure fluctuations was considered to be clinically relevant and none of the abnormalities was considered to be related to therapy. None of the changes in pulse rate (two patients, 0.4%) or body weight observed during the study was considered to be clinically relevant.

Electrocardiogram recordings made during the course of the investigation failed to show any clinically relevant new or worsening abnormalities. There was no consistent effect of the study drug on the duration of various electrocardiogram intervals and, in particular, no clinically relevant prolongations of the QTc interval were observed.

DISCUSSION

Because of the chronic nature of their disease, patients suffering from irritable bowel syndrome, who require treatment with pharmaceutical agents, will often use them over a prolonged period. Thus, long-term safety is always of major concern when a drug is intended for the treatment of patients with a chronic episodic disease such as constipation-predominant irritable bowel syndrome. The current open-label study was primarily designed to evaluate the safety of 12 months of therapy with tegaserod. This is one of the largest and longest clinical trials of any pharmacological agent recommended for treating irritable bowel syndrome. The typical length of a clinical study evaluating the safety and efficacy of modern pharmaceuticals in irritable bowel syndrome patients is 1–3 months.[15–18] In the available peer-reviewed literature (Medline search), we found only one study in which the treatment phase lasted for 6 months,[19] and another one with a

treatment period of 1 year,[20] both dealing with less than 50 patients per study. A preliminary report of another 1-year study of 714 female patients with irritable bowel syndrome has been published recently.[10]

Our data from a total of 579 patients suffering from constipation-predominant irritable bowel syndrome, treated with tegaserod at doses of either 4 mg or 12 mg daily for up to 12 months, show that the drug is well tolerated. Considering the length of the study, the overall frequency of reported adverse events is quite low, especially in terms of serious adverse events.

The results from repeated clinical laboratory evaluations, blood pressure, pulse and electrocardiogram recordings made during the study period presented no evidence of any unexpected adverse events and provided no evidence that treatment with the study drug may be unsafe. The electrocardiogram control was especially important as the gastro-prokinetic agent, cisapride, was found to cause adverse events by lengthening QT intervals.[21, 22] This effect has been explained by the experimental finding that cisapride directly inhibits the delayed rectifier potassium current in cardiac ventricular myocytes.[23] Tegaserod did not show such an effect in animal experiments,[22] nor did it produce any significant increase of the QT segment in the electrocardiograms of the patients in the current study. Cardiological safety of tegaserod is supported by the analysis of more than 10 000 electrocardiograms from various clinical studies.[5]

The comparatively high dropout numbers by the end of the study are not surprising and can be explained by several psychological and pathophysiological factors, such as the cyclic nature of chronic constipation-predominant irritable bowel syndrome, the difficulty for non-retired people with busy lifestyles to keep medical office appointments for a study during a whole year, the known tendency for subjects to stop study participation in the case of either an improved or worsening condition, etc. The early dropout rate in this study of 15% after 3 months of therapy is consistent with that observed in other short-term clinical trials in irritable bowel syndrome patients, reported at 16–24%.[15–18] The insufficient numbers of long-term trials of patients suffering from irritable bowel syndrome make it impossible to compare the discontinuation rates at the later stages of the study.

Overall, the results of this study show that tegaserod, within the range of doses studied (4–12 mg daily), is well tolerated by constipation-predominant irritable bowel syndrome patients during a 12-month period. Previous exposure to tegaserod does not result in an imbalanced frequency of adverse events compared to tegaserod-naive patients.

ACKNOWLEDGEMENT

This study was supported by Novartis Pharmaceuticals.

REFERENCES

1 Farthing MJ. Irritable bowel syndrome: new pharmaceutical approaches to treatment. Baillieres Clin Gastroenterol 1999; 13: 461–71.
2 Lee OY, Schmulson M, Mayer EA. Common functional gastrointestinal disorders: nonulcer dyspepsia and irritable bowel syndrome. Clin Cornerstone 1999; 1: 57–71.
3 Wald A. Irritable bowel syndrome. Curr Treat Options Gastroenterol 1999; 2: 13–9.
4 Serra J, Azpiroz F, Malagelada JR. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. Gut 2001; 48: 14–9.
5 Camilleri M. Tegaserod. Aliment Pharmacol Ther 2001; 15: 277–89.
6 Scott LJ, Perry CM. Tegaserod. Drugs 1999; 58: 491–6.
7 Scarpignato C, Pelosini I. Management of irritable bowel syndrome: novel approaches to the pharmacology of gut motility. Can J Gastroenterol 1999; 13(Suppl. A): 50A–65A.
8 Muller-Lissner SA, Fumagalli I, Bardhan KD, *et al.* Tegaserod, a 5-HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001; 15: 1655–66.
9 Prather CM, Camilleri M, Zinsmeister AR, *et al.* Tegaserod accelerates orocecal transit in patients with constipation–predominant irritable bowel syndrome. Gastroenterology 2000; 118: 463–8.
10 Northcutt AR, Mangel AW, Hamm LR, *et al.* Persistent placebo response during a year-long controlled trial of IBS treatment. Gastroenterology 2001; 120(Suppl. 1): 3243(Abstract).
11 Drossman DA, Thompson W, Talley NJ, *et al.* Identification of sub-groups of functional gastrointestinal disorders. Gastroenterol Int 1990; 3: 159–72.
12 Drossman DA, Richter J, Talley NJ, *et al.* The Functional Gastrointestinal Disorders, 1st edn. McLean, VA: Degnon Associates, 1994.
13 Patrick DL, Drossman DA, Frederick IO, *et al.* Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci 1998; 43: 400–11.
14 Ruigomez A, Wallander MA, Johansson S, Garcia Rodriguez LA. One-year follow-up of newly diagnosed irritable bowel syndrome patients. Aliment Pharmacol Ther 1999; 13: 1097–102.

15 Dobrilla G, Imbimbo BP, Piazzi L, Bensi G. Long-term treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo controlled clinical trial. Gut 1990; 31: 355–8.
16 Gilbody JS, Fletcher CP, Hughes IW, Kidman SP. Comparison of two different formulations of mebeverine hydrochloride in irritable bowel syndrome. Int J Clin Pract 2000; 54: 461–4.
17 Jones RH, Holtmann G, Rodrigo L, *et al.* Alosetron relieves pain and improves bowel function compared with mebeverine in female nonconstipated irritable bowel syndrome patients. Aliment Pharmacol Ther 1999; 13: 1419–27.
18 Noor N, Small PK, Loudon MA, *et al.* Effects of cisapride on symptoms and postcibal small-bowel motor function in patients with irritable bowel syndrome. Scand J Gastroenterol 1998; 33: 605–11.
19 Centonze V, Imbimbo BP, Campanozzi F, *et al.* Oral cimetropium bromide, a new antimuscarinic drug, for long-term treatment of irritable bowel syndrome. Am J Gastroenterol 1988; 83: 1262–6.
20 Mathias JR, Clench MH, Roberts PH, Reeves-Darby VG. Effect of leuprolide acetate in patients with functional bowel disease. Long-term follow-up after double-blind, placebo-controlled study. Dig Dis Sci 1994; 39: 1163–70.
21 Benatar A, Feenstra A, Decraene T, Vandenplas Y. Effects of cisapride on corrected QT interval, heart rate, and rhythm in infants undergoing polysomnography. Pediatrics 2000; 106: E85.
22 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: 82–8.
23 Drolet B, Khalifa M, Daleau P, *et al.* Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies drug-related lengthening of the QT interval. Circulation 1998; 97: 204–10.