Tegaserod for the treatment of irritable bowel syndrome and chronic constipation (Review)

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ABSTRACT

Background
IBS is a complex disorder that encompasses a wide profile of symptoms. The symptoms of chronic constipation frequently resemble those of constipation-predominant IBS. Current drug treatments for irritable bowel syndrome (IBS) are of limited value. Many target specific symptoms only. Tegaserod, a $5HT_4$ partial agonist, represents a novel mechanism of action in the treatment of IBS and chronic constipation.

Objectives
The objective of this review was to evaluate the efficacy and tolerability of tegaserod for the treatment of IBS and chronic constipation in adults and adolescents aged 12 years and above.

Search strategy
MEDLINE 1966-December 2006 and EMBASE 1980 to December 2006 were searched. The text and key words used included "tegaserod", "HTF 919", "irritable bowel", "constipation" and "colonic diseases, functional". The Cochrane Central Register of Controlled Trials, and the Inflammatory Bowel Disease Review Group Specialized Trials Register were also searched. Searches stopped on 15th December 2006. Relevant articles were retrieved, and their reference lists were also reviewed.

Selection criteria
Randomised or quasi-randomised controlled trials comparing tegaserod with placebo, no treatment or any other intervention (pharmacological or non-pharmacological) in subjects aged 12 years and above with a diagnosis of IBS or chronic constipation, focusing on clinical endpoints were considered for review.

Data collection and analysis
Study inclusion and exclusion, data extraction and quality assessment was undertaken by two authors independently. Meta-analysis was performed where study populations, designs, outcomes, and statistical reporting allowed combination of data in a valid way, using the summary statistics relative risk for dichotomous data and weighted mean difference for continuous data, both with 95% CI. Thirteen short-term placebo-controlled studies fulfilled the inclusion criteria. These were predominantly conducted in women. Ten studies evaluated the efficacy of tegaserod on global gastrointestinal (GI) symptoms in patients with constipation-predominant IBS (C-IBS). One small study evaluated safety in patients with diarrhoea-predominant IBS. Two studies evaluated the effectiveness of tegaserod for the treatment of chronic constipation.

Main results
In patients with C-IBS, the relative risk (RR) of being a responder in terms of global relief of GI symptoms during the last 4 weeks of treatment was significantly higher with both tegaserod 12 mg and 4 mg doses compared with placebo. Although the pooled results indicate statistically significant benefit with tegaserod, the a priori minimal clinically important differences set in two of three studies were not reached. The responder rate for this endpoint was also higher when considered for the first 4 weeks of treatment (tegaserod 12 mg only). Tegaserod did not significantly improve the patients' individual symptoms of abdominal pain and discomfort although bowel habit showed a statistically significant improvement with tegaserod 4 mg and there was a non-significant trend in this outcome

in favour of tegaserod 12 mg. In patients with chronic constipation, the RR of being a responder in terms of complete spontaneous bowel movements per week with tegaserod 12 mg was 1.54 (95% CI 1.35 to 1.75), WMD for this endpoint compared with placebo 0.6 (95% CI 0.42 to 0.78). Differences between tegaserod and placebo in increases in frequency of bowel movements were small (less than one per week). The proportion of patients with either diagnosis who experienced diarrhea was significantly higher in the tegaserod 12 mg group compared with placebo (RR 2.80, 95% CI 2.13 to 3.68), with a number needed to harm (NNH) of 20. Effects of tegaserod on GI symptoms such as bloating, stool consistency, and straining were not consistent across the studies.

Authors' conclusions

Tegaserod appears to improve the overall symptomatology of IBS, and the frequency of bowel movements in those with chronic constipation. The clinical importance of these modest improvements is not clear. There are currently few data on its effect on quality of life. In addition, more information is needed about its efficacy in men. It would also be of interest to know whether treatment with tegaserod leads either directly, or indirectly, to changes in visceral sensitivity or psychopathology, which are also considered important in the pathophysiology of these conditions.

PLAIN LANGUAGE SUMMARY

Tegaserod produces modest benefit when used for the treatment of constipation predominant irritable bowel syndrome and chronic constipation.

Irritable bowel syndrome (IBS) is a chronic, relapsing condition characterized by the presence of abdominal pain and disturbed bowel habit. Symptoms of chronic constipation frequently resemble those of constipation-predominant IBS. Tegaserod (4 or 12 mg/day for 12 weeks), a drug that stimulates smooth muscle in the gastrointestinal tract, produces some benefit over placebo when used to treat IBS where constipation is a major symptom. Patients taking tegaserod reported an overall improvement in their IBS symptoms, an increase in number of bowel movements per day and a reduction in number of days without bowel movements. It is not clear if tegaserod improves symptoms such as abdominal pain, bloating, stool consistency and straining. When used to treat chronic constipation, the frequency of bowel movements increased with tegaserod, but increases over those seen with placebo were small. Diarrhea occurred more often among individuals taking high dose tegaserod (12 mg/day). Further studies are needed to assess the effect of tegaserod on quality of life. More information is needed on its effectiveness in men, as most of the studies involved women.

BACKGROUND

Irritable bowel syndrome (IBS) is a chronic, relapsing condition (Talley 2002), characterised by the presence of abdominal pain and disturbed bowel habit. Symptoms of IBS sometimes overlap with other functional gastrointestinal (GI) disorders such as non-ulcer dyspepsia (Jones 2000). Irritable bowel syndrome may also co-exist with organic GI pathology, but whilst many of the symptoms are similar in nature, some occur more commonly in IBS such as easing of pain after bowel movement, looser stools and/or more frequent bowel movements at onset of pain, abdominal distension, and a feeling of incomplete emptying (Farthing 1998).

Although symptoms of the GI tract predominate in IBS, non-GI symptoms are frequent and support the diagnosis. These symptoms include lethargy, poor sleep, backache, urinary frequency, and dyspareunia (Jones 2000). About 40 to 60% of patients who seek medical advice have evidence of psychopathology (Farthing 1998).

The pattern of symptoms varies between individuals. Many patients have mild symptoms on an intermittent basis, and do not request or require drug treatment. Others can be incapacitated with persistent symptoms and seek medical advice, expecting a permanent cure (Farthing 1998). Difficulty in confirming the diagnosis may lead to increased worry and doubt. A further burden, especially in women, is the risk of unnecessary surgery such as cholecystectomy or hysterectomy, which may aggravate the existing disorder, and cause post-operative complications such as adhesions, and surgery-related changes in bowel habit (Jones 2000).

A variety of factors lead to presentation in patients with IBS. These vary in nature, e.g. from stress to precipitation by infection. Although the cause of IBS is unknown, the following pathophysiological factors have been implicated (Farthing 1995):

- disordered motility (small intestine, colon, oesophagus, and stomach);
- disordered sensation (visceral hypersensitivity); and
- central nervous system changes e.g. perception.

The diagnosis of IBS is clinically based, relying on history taking, physical examination, and where necessary, exclusion of other GI pathology. Diagnostic criteria (e.g. Manning, Rome [I, II and III])

have been introduced to aid this process, and are widely used for identifying and recruiting patients into clinical studies of interventions for IBS (Camilleri 2001; Hammer 1999). However, they are probably not used so often in clinical practice.

The aims of treatment in IBS are to improve the quality of life of patients, reduce the number of workdays missed through ill health, and to reduce the frequency of physician visits for both GI and non-GI related reasons (Jones 2000). The mainstays of treatment are explanation and reassurance regarding the nature of the condition, together with appropriate lifestyle adjustments such as dietary interventions, review of current medication, and evaluation of factors that precipitate symptoms. Drug therapy may benefit some patients although current treatments have limited value, with specific benefits being seen in a limited proportion of patients. Drug treatment of IBS can be considered in two categories (Farthing 1998): (i) treatment aimed predominantly at the gut, targeting specific dominant symptoms, using bulking agents, motility agents, and antispasmodics; and (ii) centrally acting agents (e.g. antidepressants). The site of action of antidepressants in IBS is not entirely clear.

Chronic constipation is also a common gastrointestinal complaint which clinically frequently resembles constipation predominant IBS.

Stimulation of colonic motility may be of benefit in IBS patients whose predominant symptoms are constipation-related, or in those with chronic constipation. Tegaserod (trade names Zelnorm and Zelmac) is a selective partial $5HT_4$ agonist that activates peristalsis in the smooth muscle of the GI tract accelerating gut transit. Tegaserod is an oral preparation that has been licensed for use in over 30 countries world-wide including Australia, Canada, Switzerland, the United States of America, and several Latin American countries. However in March 2007 the Food and Drug Administration (FDA) requested that the marketing of tegaserod be suspended in the USA and Canada due to safety concerns as a result of an increased rate of ischaemic cardiovascular events in patients treated with the drug (FDA 2007a). Subsequently in July 2007, the FDA announced that restricted use of tegaserod will be permitted for patients who qualify within a given protocol (FDA 2007b).

OBJECTIVES

The objective of this systematic review was to evaluate the efficacy and tolerability of tegaserod for the treatment of IBS and chronic constipation in adults and adolescents aged 12 years and above.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised or quasi-randomised controlled trials comparing tegaserod with placebo, no treatment or any other intervention (pharmacological or non-pharmacological) were included.

Studies were not excluded on the basis of publication status.

Trials were excluded if they were: studies that only administered one dose of tegaserod e.g. healthy volunteer studies; multi-dose studies that were purely pharmacokinetic; non-randomised studies. Additionally, studies conducted in children under the age of 12 years, and studies reporting only non-clinical outcomes were excluded.

Types of participants

Adults and adolescents (both genders) with a diagnosis of:

- irritable bowel syndrome according to any predefined/specified diagnostic criteria (e.g. Manning, Rome [I, II, III]); or
- chronic constipation.

Types of intervention

Trials were included if one arm of the trial received tegaserod (HTF 919), which was compared with placebo, no treatment or any other intervention (pharmacological or non-pharmacological).

Types of outcome measures

It has been recommended that the primary outcome measure in clinical trials of interventions in IBS should be some form of global assessment (van Zanten 1999). This recommendation has been adopted by the USA and European drug licensing authorities. Secondary outcomes should include a record of symptoms, and quality of life. In this review the outcomes focused on for both IBS and chronic constipation are as follows.

Main outcome measures:
Effect of treatment on
1) quality of life; and
2) gastrointestinal symptoms; both global assessment and individual symptoms including abdominal pain, distension (bloating), flatulence, bowel disturbance, constipation, diarrhoea, stool frequency, and stool consistency.

Other outcome measures:
3) Patient's compliance with treatment;
4) Adverse effects; and
5) Withdrawal (rebound) effects following discontinuation of treatment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group methods used in reviews.

The literature search aimed to locate randomised controlled trials.

Electronic searches of the following databases were conducted:

- MEDLINE (ovid 1966 to 2006)
- EMBASE (ovid 1980 to 2006)
- The Cochrane Central Register of Controlled Trials (the former Cochrane Controlled Trials Register)
- The Cochrane Inflammatory Bowel Disease Review Group Specialized Trials Register
- The USA Food and Drug Administration (http://www.fda.gov)

Search terms used in MEDLINE included the following list of Index terms and text words, which were adapted for use with other databases:
Index terms (MESH): colonic diseases, functional; serotonin agonist$
Text words: irritable bowel; irritable bowel syndrome; constipation; tegaserod; HTF 919; zelmac; zelnorm; 5HT; 5HT4

An RCT filter was applied to the electronic searches. The searches were limited to humans. No restrictions were applied with regard to language of publication or participants' age. It was our intention to translate trials reported in foreign languages; one such paper is awaiting assessment. Electronic searches were stopped on 15th December 2006. Studies identified after this date and which were considered appropriate were still assessed for eligibility.

Conference proceedings from (1) the British Society of Gastroenterology Annual Meeting (held in March), and (2) the Digestive Disease Week (the annual meeting of the American Gastroenterological Association, held in May) were searched from 1998 to 2006. Further information on unpublished studies and studies published only as abstracts was sought from the manufacturer Novartis. Reference lists from included trials were scanned to identify additional trials.

METHODS OF THE REVIEW

Methods adhered to the guidance laid out in the Cochrane Reviewer's Handbook 4.1.4. Study selection, quality assessment and data extraction were undertaken independently by two authors (BWE, WKC). Disagreements were resolved by discussion with referral to a third author if differences could not be resolved (DJM).

Quality assessment considered the four following criteria: selection, performance, attrition, and detection biases (as described in the Cochrane Reviewers' Handbook). Based on these criteria, studies were subdivided into one of three broad categories:
i. Low risk of bias (plausible bias unlikely to seriously alter the results; all quality criteria met);
ii. Moderate risk of bias (plausible bias that raises some doubt about the results; one or more criteria partly met); and
iii. High risk of bias (plausible bias that seriously weakens confidence in the results; one or more criteria not met).

Data extraction was undertaken using a data extraction form, which collected information on study methods, participants, interventions, outcome measures, and results.

Data synthesis was considered where the study populations, designs, outcomes and statistical reporting allowed combination of data in a valid way. Statistical heterogeneity was explored using the Chi square test with significance set at $P < 0.10$. Provided statistical heterogeneity was not present ($P > 0.10$), a fixed effects model was used for the analyses. If heterogeneity was present, possible sources would be investigated. The summary statistic for dichotomous data was the relative risk (RR), with 95% confidence intervals quoted. The summary statistic for continuous data was weighted mean difference (WMD). The analyses included all randomised participants in the treatment groups to which they had been allocated. Restricted analyses (excluding any unpublished studies, studies published in abstract form, studies enrolling patients using different diagnostic criteria, quasi-randomised studies) were performed where appropriate.

The analyses were conducted using review manager (RevMan) 4.2.8 software.

DESCRIPTION OF STUDIES

A total of thirteen RCTs, identified from twenty-two publications, met the inclusion criteria (Khoshoo 2006; Kamm 2005; Tack 2005; Nyhlin 2004; Johanson 2004; Kellow 2003; Fidelholtz 2002; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999a; Lefkowitz 1999b; Hamling 1998; B307). Twelve of the studies were placebo-controlled. One evaluated the addition of tegaserod to a laxative compared to a laxative alone (Khoshoo 2006).

Four studies investigating tegaserod use in patients with IBS were excluded (Bardhan 2004; Tougas 2002; Appel-Dingemanse 2000; Prather 2000). One was a non-randomised study, two RCTs reported non-clinical outcomes only, and one randomised study had no control group (See Table of characteristics of excluded studies).

Of the thirteen RCTs that met the inclusion criteria, nine studies were reported as fully published papers. Data from three studies were published in abstracts (Lefkowitz 1999a; Lefkowitz 1999b; Hamling 1998), and in information provided in the Briefing Document submitted by the manufacturers to the Federal Drug Ad-

ministration (FDA) in 2000 (Novartis 2000). No publications of the remaining study, B307, were identified other than the information provided in the FDA Briefing Document (Novartis 2000). Further information on the trials published only as abstracts and the unpublished study (B307) was sought from the manufacturers (USA contact), but none was received.

Ten studies were conducted in a total of 8,589 patients with constipation-predominant IBS (C-IBS) (Khoshoo 2006; Tack 2005; Nyhlin 2004; Kellow 2003; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999a; Lefkowitz 1999b; Hamling 1998; B307). C-IBS was diagnosed using the Rome criteria; Rome I in six studies (Novick 2002; Muller-Lissner 2001; Lefkowitz 1999a; Lefkowitz 1999b; Hamling 1998; B307), and Rome II in four (Khoshoo 2006; Tack 2005; Nyhlin 2004; Kellow 2003). Two studies enrolled a total of 2612 patients with chronic constipation, defined as an average of fewer than three complete spontaneous bowel movements per week, together with at least one of the following symptoms occurring at least 25% of the time: straining, incomplete evacuation, very hard and/or hard stools (Kamm 2005; Johanson 2004). One study was conducted in 86 patients with diarrhoea-predominant IBS (D-IBS), based on Rome I diagnostic criteria (Fidelholtz 2002).

The population studied was predominantly women (refer to Table of included studies). Two studies enrolled only women (Tack 2005; Novick 2002). Reported age of patients in treatment groups of the included studies ranged from a mean of approximately 36 years to 48 years (see Table of included studies), except for the study evaluating tegaserod in combination with a laxative which was undertaken in adolescents with mean age 15 years (Khoshoo 2006).

The duration of C-IBS in studies including adults varied, ranging from means of 7.2 to 17.4 years (Tack 2005; Nyhlin 2004; Kellow 2003; Fidelholtz 2002; Novick 2002; Lefkowitz 1999b; B307) or medians of 8.2 to 10.0 years (Muller-Lissner 2001). Mean duration of C-IBS in the adolescents evaluated was 7 months (Khoshoo 2006). The duration of constipation in the two studies that evaluated this condition was 15 years (Kamm 2005) and 19 years (Johanson 2004).

To qualify for enrolment several studies specified a minimum duration of symptoms of 3 months (Fidelholtz 2002; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307) or 6 months (Kamm 2005; Johanson 2004). Patients also had to fulfill certain symptom criteria in most of the studies. In four C-IBS studies, patients were required to have two of three constipation criteria, which were fewer than 3 bowel movements per day, hard or lumpy stools, or straining at least 25% of the time (Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). Another C-IBS study required that patients had C-IBS and abdominal/pain with at least two other symptoms for at least 12 weeks during the previous 12 months, and had used non-drug therapy for at least 2 months without adequate relief of their symptoms (Tack 2005). Patients in the Fidelholtz 2002 study were required to have two of three diarrhoea criteria, which were more than 3 bowel movements per day, loose or watery stools, or urgency at least 25% of the time. Refer to the Table of included studies for more information.

Exclusion criteria were listed in the fully published studies. Patients were generally excluded if they had organic bowel disease; were planning to use drugs that affect GI motility and/or perception; had cathartic colon, or other conditions known to affect bowel transit (Khoshoo 2006; Tack 2005; Kamm 2005; Nyhlin 2004; Johanson 2004; Kellow 2003; Fidelholtz 2002; Novick 2002; Muller-Lissner 2001).

Study design

Of the ten studies evaluating tegaserod for the treatment of C-IBS, two were phase II dose-finding studies (Lefkowitz 1999a; Hamling 1998), which evaluated daily doses of 1 mg, 4 mg, 12 mg, and 24 mg of tegaserod. Three (Muller-Lissner 2001; Lefkowitz 1999b; B307) were the original phase III studies of the tegaserod clinical trial programme. Of these, Muller-Lissner 2001 and Lefkowitz 1999b were identical in design, evaluating two fixed daily doses of 4 mg and 12 mg. B307 was also similar in design except that the tegaserod 12 mg treatment arm started with a dose of 4 mg, which could be increased to 12 mg according to response (the dose was increased from 4 mg to 12 mg in 65% of patients after the first month of double-blind treatment). The remaining five studies in C-IBS (Khoshoo 2006; Tack 2005; Nyhlin 2004; Kellow 2003; Novick 2002) evaluated the 12 mg dose of tegaserod only. Each of the studies was short-term with treatment periods of between 4 and 12 weeks. This was preceded by treatment-free periods of 2 or 4 weeks, and in three studies, was followed by a 4-week withdrawal period (Nyhlin 2004; Kellow 2003; Novick 2002). Tack 2005 considered the effectiveness of repeated tegaserod treatment in patients who had responded to the first course of tegaserod (those with at satisfactory relief of their overall symptoms or of abdominal pain and discomfort at least 50% of the time), but who experienced recurrence of symptoms after treatment withdrawal.

Both studies of tegaserod for chronic constipation evaluated 4 mg and 12 mg doses for 12-week double-blind treatment periods (Kamm 2005; Johanson 2004). One of the studies also had a 4-week withdrawal period (Johanson 2004).

In the D-IBS population studied by Fidelholtz 2002, 8 weeks' treatment with 4 mg and 12 mg daily doses of tegaserod was evaluated.

All daily doses of tegaserod across all trials were taken in two divided doses.

OUTCOMES

Patients recorded their IBS symptoms in paper diaries (Khoshoo 2006; Kamm 2005; Johanson 2004; Kellow 2003; Fidelholtz 2002; Muller-Lissner 2001; Lefkowitz 1999b), in an electronic diary (Tack 2005), or using a touch tone telephone system (Nyhlin 2004; Novick 2002).

C-IBS

Nine studies that enrolled patients with C-IBS evaluated a global outcome (Subjects Global Assessment [SGA]) encompassing GI symptoms (SGA of Relief, or SGA of GI symptoms). The question asked of patients in order to determine the proportion of responders for these endpoints differed among the studies. In the dose-ranging tegaserod studies (Lefkowitz 1999a; Hamling 1998) patients were asked, "Compared to the way you usually felt during the 3 months before you entered the study, are your overall GI symptoms over the past 4 weeks completely, considerably, somewhat relieved, unchanged or worse"? Patients with complete or considerable relief at study endpoint (last 4 weeks of treatment) were called responders.

Novick 2002, Muller-Lissner 2001, Lefkowitz 1999b and B307 asked patients, "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. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week"? Possible answers were: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Patients with complete or considerable relief at least 50% of the time, or with somewhat relief 100% of the time at study endpoint were called responders (the study endpoint was defined as the last 4 available weekly SGA scores, or all weekly SGA scores if fewer than 4 were available).

Tack 2005, Nyhlin 2004 and Kellow 2003 asked, "Over the past week do you consider that you have had satisfactory relief from your IBS symptoms" over the first four weeks of double-blind treatment. Patients answered yes or no. Patients with at least 75% (Tack 2005; Kellow 2003) or 50% (Nyhlin 2004) of 'yes' responses were called responders.

Three of these studies also specified what they considered to be a minimal clinically important difference in the proportion of responders for SGA of Relief between treatments (Kellow 2003; Novick 2002; Muller-Lissner 2001). Refer to the table of included studies.

Other outcomes reported in these studies were patients' assessment of:

- abdominal pain and discomfort (7 studies; Tack 2005; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999a; Lefkowitz 1999b; Hamling 1998; B307);
- bowel habit (4 studies; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307 - This endpoint encompassed intensity of abdominal discomfort/pain; intensity of abdominal bloating; number of bowel movements; and average daily stool consistency);
- satisfaction with bowel habit (1 study; Novick 2002);
- constipation (3 studies; Tack 2005; Lefkowitz 1999a; Hamling 1998);
- GI symptoms such as bloating, bowel movements (7 studies; Tack 2005; Nyhlin 2004; Kellow 2003; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307); and
- quality of life (Work Productivity and Activity Impairment questionnaire for IBS) - 1 study (Tack 2005; data were reported in a separate paper [Reilly 2005]).

Khoshoo 2006 considered the effectiveness of adding tegaserod to laxative treatment in terms of abdominal pain and bowel movements per week.

Chronic constipation

Both studies evaluated the same outcomes; the responder rate for complete spontaneous bowel movements (CSBM, defined as an increase of one or more CSBM per week), changes in frequency of bowel movements, time to first CSBM, stool form, and laxative use (Kamm 2005; Johanson 2004). Changes in other symptoms were also reported; sensation of complete evacuation, straining, and global measures (bothersomeness of constipation, abdominal bloating/distension, and satisfaction with bowel habit).

D-IBS

Fidelholtz 2002 focussed on safety and tolerability of tegaserod with respect to effects on GI symptoms (e.g. number of bowel movements, days with loose or watery stools, and stool consistency score).

METHODOLOGICAL QUALITY

Quality assessment of only the fully published studies was performed, as there was insufficient information to assess the quality of the studies published in abstract form. All studies were described as randomised. Six studies described the method of randomisation (Khoshoo 2006; Tack 2005; Kamm 2005; Nyhlin 2004; Johanson 2004; Kellow 2003). Allocation of treatment was concealed in three studies (Tack 2005; Kamm 2005; Johanson 2004) but this was unclear in the remainder. Using the Cochrane criteria for selection, performance, detection, and attrition bias, studies with adequate allocation concealment had low risk of selection bias (Tack 2005; Kamm 2005; Johanson 2004) whereas others had at least moderate risk of bias.

Performance and detection bias was possible in all studies. Although five of the studies stated that tegaserod and placebo tablets were identical in appearance (Novick 2002; Fidelholtz 2002; Muller-Lissner 2001), or that double-dummy blinding was used (Johanson 2004; Kamm 2005), it is unclear whether personnel providing care and/or assessing outcomes were blind to assigned treatment. Two studies report that all personnel were blinded to assigned treatment (Kellow 2003; Nyhlin 2004). The method of blinding is not explained in Tack 2005. Treatment was not blinded in Khoshoo 2006. Attrition bias is unlikely as each study used intention to treat (ITT) analysis, stated all withdrawals and the

reasons for withdrawals, with the exception of Fidelholtz 2002 where only withdrawals due to adverse events were listed.

In all but Fidelholtz 2002 the treatment groups within each study were comparable at baseline. There are concerns regarding the comparability of the treatment groups at baseline in the Fidelholtz 2002 study. The mean number of bowel movements per week, ($P < 0.02$) and the mean number of days with 4 or more bowel movements per week, ($P < 0.05$) were significantly higher in the placebo group than either of the tegaserod groups (4 mg and 12 mg). This may introduce considerable bias in view of the small size of the study (n = 86).

In 12 studies the study sponsor was the manufacturer, Novartis. The Khoshoo 2006 study received no external funding.

RESULTS

C-IBS

SGA OF RELIEF

Data from four studies that compared tegaserod 12 mg with placebo (n = 3194) and reported responder rates for the last 4 weeks of double-blind (DB) treatment were combined (Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). Individually, of the four studies, statistically significant benefit was apparent in two (Muller-Lissner 2001; Lefkowitz 1999b), with a non-significant trend for benefit with tegaserod seen in the other two (Novick 2002; B307); see Table 01. The Chi square test indicated no significant heterogeneity between the four studies. Therefore, the fixed-effects model was used in the meta-analysis. The RR for being a responder in terms of SGA of Relief at endpoint with tegaserod 12 mg compared with placebo was 1.19 (95% CI 1.09 to 1.29), indicating statistically significant benefit. The risk difference (RD) for this comparison was 0.07 (95% CI 0.03 to 0.10), with a number needed to treat (NNT) of 14. When a restricted analysis was performed, combining data from the two fully published studies, the RR was 1.16 (95% CI 1.04 to 1.29) indicating statistically significant benefit. The RD for this comparison was 0.06 (95% CI 0.02 to 0.10), with a NNT of 17.

Complete numerical results were not reported for each treatment group in the publications of Lefkowitz 1999a and Hamling 1998.

For the comparison of tegaserod 4 mg with placebo, data from three studies (n = 1685) were pooled (Muller-Lissner 2001; Lefkowitz 1999b; B307). Of the three studies, a statistically significant benefit was apparent in one (Muller-Lissner 2001), and a non significant trend in favour of tegaserod in the other two (Lefkowitz 1999b; B307). The pooled data show that the RR of SGA of Relief at endpoint for tegaserod 4 mg compared with placebo was 1.15 (95% CI 1.02 to 1.31), indicating statistically significant benefit. The RD for this comparison was 0.05 (95% CI 0.01 to 0.10), with a NNT of 20. The same three studies compared 12 mg and 4 mg tegaserod doses (n = 1682). Pooled data from these were non-significant, RR 1.09 (95% CI 0.97 to 1.22).

When all tegaserod doses were combined and compared with placebo (n = 4040), the RR of being a responder at endpoint was 1.17 (95% CI 1.08 to 1.27), indicating statistically significant benefit (Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). The RD was 0.06 (95% CI 0.03 to 0.09), with a NNT of 17. Although the pooled results indicate statistically significant benefit with tegaserod, the a priori minimal clinically important differences set by Novick 2002 and Muller-Lissner 2001 in their studies were not reached.

Data from two other studies that used a different definition of responder and at a different time point (weeks 1-4 of DB treatment) were pooled separately (Tack 2005; Kellow 2003). The RR for being a responder in terms of SGA of Relief for weeks 1-4 of DB treatment with tegaserod 12 mg compared with placebo was 1.46 (95% CI 1.28 to 1.66), indicating statistically significant benefit. The RD for this comparison was 0.12 (95% CI 0.08 to 0.16), with a NNT of 8 (n = 3180). The results for the Kellow 2003 study met the pre-defined criteria for a minimal clinically important difference between groups.

ABDOMINAL PAIN AND DISCOMFORT

Three studies reported responder rates, which were combined in a meta-analysis for both 12 mg and 4 mg doses vs placebo (Muller-Lissner 2001; Lefkowitz 1999b; B307); see Table 02. A responder was a patient who fulfilled the adjustment rules and the following criteria: at least 20 mm and 40% reduction in mean VAS score at endpoint compared to baseline. Individually, the three studies showed disparate results with B307 suggesting no benefit with either tegaserod dose, and Muller-Lissner 2001and Lefkowitz 1999b showing a non-significant trend in favour of tegaserod (both doses). Due to the significant heterogeneity among the studies, a random-effects model was used in the meta-analysis. The RR for being a responder with tegaserod 12 mg compared with placebo (n = 1675) was 1.16 (95% CI 0.89 to 1.51), and 1.10 (95% CI 0.82 to 1.49) for tegaserod 4 mg compared with placebo (n = 1685). Both results show a non-significant difference between tegaserod and placebo treatment. When the 12 mg and 4 mg tegaserod doses were compared (n = 1682), the results were non-significant, RR 1.05 (95% CI 0.90 to 1.23). Pooling all tegaserod doses compared with placebo (n = 2521) gave a RR of being a responder of 1.13 (95% CI 0.85 to 1.51), which was also not statistically significant.

The SGA of abdominal pain and discomfort was also a planned endpoint in the Lefkowitz 1999a and Hamling 1998 studies, but no numerical data were found for the individual tegaserod groups in these studies. Novick 2002 reported mean score differences rather than responder rates, which showed significant improvement from baseline with tegaserod 12 mg compared with placebo (-1.01 vs -0.80, $P < 0.003$).

Tack 2005 reported the proportion with satisfactory relief of abdominal pain and discomfort (75% of the time) over the 4-week treatment period. The difference between tegaserod 12 mg and placebo groups was statistically significant (9.1%, 95% CI 5.2 to 13.0). The proportion of patients reporting improvement in these symptoms (of one point or more on a 7-point scale) was also higher with tegaserod than placebo (52.5% vs 42.8%, P < 0.001).

Khoshoo 2006 considered abdominal pain on a scale of 0-10 (none to worse possible); see Table 09. The mean pain score was lower with combined tegaserod and laxative treatment than with laxative alone at 4 weeks (4.29 vs 6.15, P < 0.05). The proportion of patients with good pain reduction (defined as a reduction in pain score of 3 or more points compared with pre-treatment) was also higher with combination treatment (66.7% vs 18.5%, P < 0.05).

BOWEL HABIT

Three studies reported responder rates, which were combined in a meta-analysis for both 12 mg and 4 mg doses vs placebo (Muller-Lissner 2001; Lefkowitz 1999b; B307); see Table 03. A responder was a patient who fulfilled the adjustment rules and the following criteria: at least 20 mm and 40% reduction in mean VAS score at endpoint compared to baseline. Individually, of the three studies, B307 suggested no benefit with either tegaserod dose, and Muller-Lissner 2001 and Lefkowitz 1999b showed a non significant trend in favour of tegaserod (both doses). No statistically significant heterogeneity was detected. Pooled data from three studies (n = 1685) indicate that patients treated with tegaserod 4 mg were significantly more likely than placebo to be responders, RR 1.21 (95% CI 1.03 to 1.43). The RD for this comparison was 0.05 (95% CI 0.01 to 0.09), with a NNT of 20. The RR for tegaserod 12 mg compared with placebo (n = 1675) was non-significant, 1.10 (95% CI 0.93 to 1.31). When both tegaserod doses were compared, the result was non-significant, RR 0.91 (95% CI 0.78 to 1.07). When all tegaserod doses were pooled and compared with placebo (n = 2521), the RR of being a responder was 1.16 (95% CI 1.00 to 1.34) which does not indicate statistical significance.

Novick 2002 reported the mean score difference from baseline to endpoint on a 7-point ordinal scale, which was reduced to a significantly greater extent with tegaserod 12 mg compared with placebo (-1.30 vs -0.95, P < 0.001).

SATISFACTION WITH BOWEL HABIT

Novick 2002 reported response rates at months one, two and three (see Table 04). A responder was a patient who was 'very satisfied' or 'somewhat satisfied' at 50% of assessments. The response rates at all time points were significantly higher in the tegaserod 12 mg group than with placebo.

CONSTIPATION

Constipation was a planned endpoint in four studies. Hamling 1998 reported responder rates but not for the ITT population, and only for pooled tegaserod groups. A responder was a patient with considerable or complete relief at study endpoint (last 4 weeks of treatment). No numerical data were presented for this endpoint in the publications related to Lefkowitz 1999a.

Tack 2005 reported the proportion with satisfactory relief of constipation (75% of the time), which was higher with tegaserod 12 mg than placebo (39.4% vs 25% respectively, P < 0.001).

Khoshoo 2006 reported the change in frequency of bowel movements per week. This was higher following combined tegaserod and laxative treatment than with laxative alone at 4 weeks (mean frequency 6.57 vs 5.04, P < 0.05).

OTHER GI SYMPTOMS

Muller-Lissner 2001, Lefkowitz 1999b and B307 recorded changes in bloating, abdominal pain/discomfort, bowel movements and stool consistency. The number of days without bowel movements was reduced and the number of bowel movements increased significantly with tegaserod 12 mg compared with placebo. There was a non-significant trend towards reduction in days with significant abdominal pain and discomfort, days with significant bloating, and days with hard or very hard stools in both tegaserod groups compared with placebo. Lefkowitz 1999a reported scores for days with pain, bloating, and bowel movements according to whether they were deemed to be responders, not by treatment group.

Tack 2005, Nyhlin 2004, Kellow 2003 and Novick 2002 also reported results for some individual GI symptoms. Data from the studies were not pooled because although apparently similar the outcomes were not consistently defined, nor were they measured across the same treatment weeks. Tack 2005 reported statistically significant differences forimprovements in bloating and stool consistency in favour of tegaserod. Nyhlin 2004 reported that days with hard or very hard/lumpy stools were significantly fewer with tegaserod 12 mg compared with placebo and days with loose or watery stools higher. There were no significant differences identified between groups in bloating or days with at least moderate abdominal pain or discomfort. Days with straining and a sensation of incomplete evacuation were significantly reduced with tegaserod 12 mg compared with placebo; days with urgency were significantly reduced with tegaserod during weeks 1-4 but not weeks 9-12 (Nyhlin 2004).

Kellow 2003 reported that days with hard or lumpy stools and days with at least moderate abdominal pain and discomfort were significantly fewer with tegaserod 12 mg compared with placebo, with no significant differences identified between groups in bloating, number of bowel movements, stool consistency, urgency, or straining. In the Novick 2002 study, the number of bowel movements increased significantly, and bloating, straining, and stool consistency scores fell significantly with tegaserod 12 mg from baseline compared with placebo.

QUALITY OF LIFE

Reilly 2005 reported results of the Work Productivity and Activity Impairment questionnaire for IBS in the 63% of patients included

in the Tack 2005 study who were employed. Only data for the first 4-week treatment period are available. These show reductions with tegaserod 12 mg compared with placebo of 2.6% in absenteeism (P = 0.004), 5.4% in presenteeism (P < 0.0001), 6.3% in work productivity loss (P < 0.0001), and 5.8% in daily activity impairment (P < 0.0001).

REPEAT TREATMENT
In the Tack 2005 study, statistically significant benefit for all GI outcomes was reported in patients who had a second course of tegaserod treatment compared with placebo (see Table 12).

Chronic constipation studies
Both of the chronic constipation studies reported the responder rate for complete spontaneous bowel movements (CSBM, defined as an increase of one or more CSBM per week) following 12 weeks treatment; see Table 10. Data were combined for the tegaserod 12 mg group compared with placebo (n = 1745). The RR of responding to tegaserod 12 mg was 1.54 (95% CI 1.35 to 1.75), which indicates a statistically significant benefit. The RD for this comparison was 0.15 (95% CI 0.11 to 0.20), giving a NNT of 7 to have a mean increase of one bowel movement per week. Only Johanson 2004 reported data for the 4 mg dose at 12 weeks which showed a significantly higher responder rate than for placebo. Kamm 2005 reported that the difference between tegaserod 4 mg and placebo was not statistically significant, but did not report the responder rates.

Weekly bowel frequency (CSBM, spontaneous bowel movements, and bowel movements) increased in both tegaserod groups and the placebo groups. The difference between tegaserod 12 mg and placebo was statistically significant for CSBM (WMD [fixed effects] 0.6, 95% CI 0.42 to 0.78); SBM (WMD 0.91, 95% CI 0.59 to 1.23); and for bowel movements (WMD 0.75, 95% CI 0.46 to 1.05). The difference between tegaserod 4 mg and placebo were also statistically significant for CSBM (WMD [fixed effects] 0.44, 95% CI 0.26 to 0.62); SBM (WMD 0.73, 95% CI 0.41 to 1.05); and for bowel movements (WMD 0.58, 95% CI 0.28 to 0.88). Differences between tegaserod 12 mg and tegaserod 4 mg were not statistically significant.

Other GI symptoms
Several other outcomes were reported in both studies, the results of which are all of questionable clinical significance (Kamm 2005; Johanson 2004). The median time to first CSBM was significantly shorter with tegaserod 4 mg and 12 mg than with placebo (see Table 11). Stool form changed significantly in the direction of unformed stools with tegaserod compared with placebo but changes were less than one point on an 8-point scale. There was a trend towards greater reduction in straining scores (measured on a 3-point scale), and in days with too much straining.

The proportion of days per week when laxatives were used was less (Kamm 2005) - absolute difference 0.2 days (tegaserod 4 mg) and 0.5 (tegaserod 12 mg) compared with placebo. Johanson 2004 measured the use of rescue laxative medication; differences between groups were not significantly different (absolute differences 0.1 and 0 for tegaserod 4 mg and 12 mg compared with placebo respectively).

Bothersomeness of constipation, abdominal bloating/distension, or abdominal pain/discomfort were measured on a 5-point scale (none to a very great deal); scores fell in all groups. No score change was greater than 0.7 although the differences were statistically significant in favour of both tegaserod groups for these three outcomes. Satisfaction with bowel habit, also measured on a scale of 0-5, increased to a greater extent with tegaserod although none of the score changes were greater than 0.8.

TOLERABILITY (all studies)
Numerical data for each treatment group (ITT analysis) were reported for eight studies (Tack 2005; Kamm 2005; Nyhlin 2004; Johanson 2004; Kellow 2003; Fidelholtz 2002; Novick 2002; Muller-Lissner 2001). See Tables 5 to 8 (Table 05; Table 06; Table 07; Table 08).

Data on adverse events reported in the six 12-week studies that were conducted in individuals with C-IBS or chronic constipation were pooled (Kamm 2005; Nyhlin 2004; Johanson 2004; Kellow 2003; Novick 2002; Muller-Lissner 2001). A consistent effect on diarrhoea was seen in the six studies. The RR of diarrhoea with tegaserod 12 mg compared with placebo (n = 5010) was significantly higher, 2.80 (95% CI 2.13 to 3.68). The RD for this comparison was 0.05 (95% CI 0.04 to 0.06), with a number needed to harm (NNH) of 20. The RR of diarrhoea was also higher with tegaserod 4 mg than with placebo (3 studies; Kamm 2005; Johanson 2004; Muller-Lissner 2001); RR 1.70 (95% CI 1.12 to 2.59), RD 0.02 (95% CI 0.00 to 0.04). Of the other pooled adverse events (from five or six of the studies), none of these occurred with a significantly higher frequency with tegaserod 12 mg although there was a trend in that direction; headache RR 1.07 (95% CI 0.92 to 1.24); abdominal pain RR 1.03 (95% CI 0.83 to 1.28); and nausea RR 1.21 (95% CI 0.93 to 1.57).

No adverse effects were reported in Khoshoo 2006.

Because other GI stimulants are known to have cardiac effects, e.g. cisapride (also a 5HT4 partial agonist), the electrocardiographic effects of tegaserod were investigated in studies Muller-Lissner 2001, Lefkowitz 1999b and B307 (n = 2525) and the results have been published (Morganroth 2002). The data from these short-term studies did not identify statistically significant differences between tegaserod 4 mg or 12 mg and placebo groups in the proportion of patients with prolonged QTc intervals, or the overall frequency of electrocardiographic abnormalities. However in March 2007 the FDA requested that the marketing of tegaserod be withdrawn due to an increased rate of ischaemic cardiovascular events in patients treated with the drug, although these data are not published in other trial reports considered in this review (FDA 2007a).

DISCUSSION

In individuals, predominantly women, with C-IBS tegaserod 12 mg and 4 mg significantly improved patients global assessment of IBS symptomatology compared with placebo. Tegaserod did not significantly improve patients' abdominal pain and discomfort although bowel habit showed a significant improvement with tegaserod 4 mg and there was a non-significant trend in favour of tegaserod 12 mg compared with placebo. When GI symptoms were assessed separately, those indicative of GI motility such as number of bowel movements and days without bowel movements were generally improved with tegaserod, whereas effects of treatment on symptoms such as bloating and stool consistency and straining were not consistent across the studies.

When used for the treatment of chronic constipation tegaserod 12 mg increased the frequency of weekly bowel movements although differences between tegaserod 12 mg and placebo groups were small. Improvements in other symptoms such as straining, bloating, and abdominal pain/discomfort were also minor.

In the C-IBS studies the effect of publication bias was explored using a restricted analysis of pooled SGA of Relief at endpoint data for tegaserod 12 mg vs placebo. The direction of the evidence was the same when the unpublished study (B307) and the study published as an abstract were excluded from the analysis, although the NNT was higher when the unpublished studies were excluded (NNT 17 vs 14). The comparison of the 4 mg and 12 mg doses of tegaserod did not show a clear distinction between the two doses.

Whilst the meta-analysis has shown a significant treatment effect with both tegaserod doses compared with placebo, such a consistent effect was not seen in the individual studies. In particular, a significant difference between tegaserod 4 mg or 12 mg and placebo groups was not observed in B307, the results of which have not been published other than in the FDA briefing document. It should be noted that in study B307, the patients in the higher dose group started off with a dose of 4 mg, which was increased to 12 mg in 65% patients. In the Lefkowitz 1999b study, only published in abstract form, a significant difference was seen with tegaserod 12 mg compared with placebo, but not with tegaserod 4 mg. Lefkowitz 1999b was the first phase III study to be completed, which prompted a change in the definition of responder because a significant treatment effect was not seen with tegaserod compared with placebo (Novartis 2000). The data listed in this review are the results of the retrospective analysis of results from the Lefkowitz 1999b study that was performed when the revised definition of responder was agreed, which reduced the threshold for response. The definition of responder is described in the outcomes section.

With regard to tolerability in the studies, diarrhoea occurred with a significantly higher incidence in the tegaserod 12 mg group, which is not surprising given the drug's mode of action. The balance of improving symptoms of C-IBS without causing diarrhoea may be difficult to achieve. It was not possible to pool data for the 4 mg dose as the two studies contributing the relevant data enrolled different study populations (diarrhoea-predominant IBS in Fidelholtz 2002, and constipation-predominant IBS in Muller-Lissner 2001). The other documented events (abdominal pain, headache, nausea), represent some of the typical GI and extra-intestinal symptoms of IBS. Because other GI stimulants are known to have cardiac effects, e.g. cisapride (also a $5HT_4$ partial agonist), the electrocardiographic effects of tegaserod were investigated in studies Muller-Lissner 2001, Lefkowitz 1999b and B307 (n = 2525) and the results have been published (Morganroth 2002). The data from these short-term studies did not identify statistically significant differences between tegaserod 4 mg or 12 mg and placebo groups in the proportion of patients with prolonged QTc intervals, or the overall frequency of electrocardiographic abnormalities. However in March 2007 the FDA requested that the marketing of tegaserod be withdrawn due to an increased rate of ischaemic cardiovascular events in patients treated with the drug (FDA 2007a). Subsequently in July 2007, the FDA announced that restricted use of tegaserod will be permitted for patients who qualify within a given protocol (FDA 2007b). The treatment investigational new drug protocol specifies that tegaserod be used to treat irritable bowel syndrome with constipation and chronic idiopathic constipation in women younger than 55 who meet specific guidelines. In addition to the age and gender restrictions, the protocol limits use of the drug to those with C-IBS or chronic idiopathic constipation whose physicians decide the drug is medically necessary. Patients must sign consent materials to ensure they are fully informed of the potential risks and benefits of tegaserod (FDA 2007b).

Individuals enrolled in the IBS studies included in this review fulfilled Rome diagnostic criteria, which were originally developed in order to allow greater comparability of drug effects between studies of treatments for IBS. Although the Rome criteria are frequently used entry criteria for such clinical studies, in clinical practice, studies evaluating diagnosis of IBS in primary care have found that set diagnostic criteria were rarely used (Thompson 1997) and that many patients given a diagnosis of IBS did not fulfill these criteria (Robinson 2001). Rome criteria have also been criticised for not encompassing some clinical patterns seen by clinicians (Camilleri 2001), such as not taking into account postprandial exacerbation of symptoms; excluding subgroups based on predominant bowel dysfunction; and not encompassing patients in whom functional, painless diarrhoea may be associated with postprandial urgency, borborygmi, and a sense of incomplete rectal evacuation. It is difficult to determine how representative the patients enrolled in the clinical trials are of those who present in the primary care setting with symptoms of IBS.

IBS is a complex disorder that encompasses a wide profile of symptoms. Tegaserod appears to improve the overall symptomatology of IBS, and increase the number of bowel movements in chronic constipation, but the clinical significance of these modest changes is unclear. There are currently few data on tegaserod's effect on

quality of life. In addition, more information is needed about its efficacy in men. It would also be of interest to know whether treatment with tegaserod leads either directly, or indirectly, to changes in visceral sensitivity or psychopathology, which are also considered important in the pathophysiology of this condition.

AUTHORS' CONCLUSIONS

Implications for practice

For women with constipation-predominant IBS, tegaserod offers modest improvement of their global GI symptoms, but may not address symptoms of abdominal pain and discomfort. The treatment may be an option for short-term relief of symptoms. The FDA is permitting the restricted use of Tegaserod under a treatment investigational new drug protocol. Tegaserod may be used to treat C-IBS and chronic idiopathic constipation in women under 55 where no comparable or satisfactory alternative drug is available. The patient's physician must decide the drug is medically necessary and patients must sign a consent form indicating that they are fully informed of the potential risks and benefits of tegaserod.

In practice the division between constipation-predominant and diarrhoea-predominant IBS may not be clear-cut in some patients. It is not yet apparent whether there is a sub-group of women with C-IBS who may gain most benefit from tegaserod treatment.

For women with chronic constipation tegaserod increases bowel frequency relative to placebo although the net increase is less than one bowel movement per week.

Implications for research

Ongoing research aims to investigate the existence of a rebound effect on withdrawal of tegaserod, and the effects of withdrawal on symptomatic control. Longer-term studies would help determine the duration of benefit with tegaserod treatment, and its safety with prolonged use. More information on the effects of tegaserod treatment on quality of life of patients, and on medical consultation rates, as well as comparative studies of tegaserod with established IBS treatments would be valuable in defining its place in therapy.

POTENTIAL CONFLICT OF INTEREST

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	B307
Methods	Randomised double-blind placebo-controlled parallel group 67-centre study. Duration: 16 weeks (4 treatment-free baseline, 12 DB treatment)
Participants	M/F >=18 years (85% F). Mean age (SD) 45 (13) years. C-IBS (Rome I criteria). Minimum of 3 months symptoms. Duration of IBS (mean in months, SD) 166 (154).
Interventions	Tegaserod 4mg (n=283) Tegaserod 4-12mg (n=277) Placebo (n=285) Other permitted treatments: chronic stable treatment with fibre or bulking agents.
Outcomes	SGA of Relief (responder rate). Abdominal pain and discomfort. Bowel habit. GI symptoms.
Notes	No publications identified for this study. Data taken from Novartis 2000.
Allocation concealment	D – Not used

Study	Fidelholtz 2002
Methods	Randomised double-blind placebo-controlled parallel group study. Duration: 10 weeks (2 treatment-free baseline, 8 DB treatment)
Participants	M/F >18 years (67.4% F). Mean age (range 21-77 years); 41.4 T12mg, 47.3 T4mg, 48.5 Plac. D-IBS (Rome I criteria). Minimum of 3 months symptoms. Duration of IBS (mean, in years); 9.8 T12mg, 11.5 T4mg, 10.5 Plac. Organic disease excluded. Exclusion criteria: Significant changes in bowel habit in previous 3 months; non-IBS conditions affecting bowel transit; cathartic colon; drugs affecting GI motility and/or perception.
Interventions	Tegaserod 4mg (n=35) Tegaserod 12mg (n=34) Placebo (n=17) Other permitted treatments: loperamide for diarrhoea, chronic stable doses of bulking agents or antidepressants
Outcomes	Safety. Adverse events. No efficacy parameters reported.
Notes	At baseline number of bowel movements per week, and number of days with 4 or more bowel movements per week both significantly higher in the placebo group than the tegaserod groups.
Allocation concealment	B – Unclear

Study	Hamling 1998
Methods	Randomised double-blind placebo-controlled parallel group dose-ranging 16-centre study. Duration 20 weeks.
Participants	M/F >= 18 years (92% F).

Characteristics of included studies (*Continued*)

	Mean age 44 years. C-IBS (Rome I criteria).
Interventions	Tegaserod 1mg, 4mg, 12mg, 24mg - started with 1mg, up-titrated according to clinical response (n=?) Placebo (n=?) Total n=123, randomised 2:1 T:P
Outcomes	SGA of GI symptoms. Abdominal discomfort. Constipation.
Notes	Responder rates determined for each endpoint. Abstract publication of study only. No details of statistical or other analyses used.
Allocation concealment	D – Not used

Study	**Johanson 2004**
Methods	Randomised double-blind placebo-controlled parallel group 105-centre study. Duration 18 weeks (2 weeks treatment-free baseline, 12 weeks DB treatment, 4 weeks optional withdrawal).
Participants	M/F >= 18 years (90% F). Mean age 47 years. Constipation for 6 months or more, mean 19 years (defined as an average of less than three complete spontaneous bowel movements per week, together with at least one of the following symptoms occurring at least 25% of the time: straining, incomplete evacuation, very hard and/or hard stools). Exclusion criteria: Constipation caused by a known disease of the colon, pelvic floor dysfunction, metabolic disorders, neurological disorders, or other significant disease that may have prevented patients from completing the study, use of medications that affect GI function.
Interventions	Tegaserod 4mg (n=450) Tegaserod 12mg (n=451) Placebo (n=447)
Outcomes	Complete spontaneous bowel movements (responder rate). Weekly number of bowel movements (including complete spontaneous, and spontaneous). Time to first complete spontaneous bowel movement. Stool form. Change in other symptoms (sensation of complete evacuation, straining, bothersomeness), satisfaction, laxative use.
Notes	Responders were defined as those with a mean increase of one or more complete spontaneous bowel movements per week compared with the baseline period. Stool form assessed using the 8-point Bristol Stool Form chart (0=separate hard lumps, 7=watery, unformed stools). Straining: 3-point scale (0=none, 2=too much). Bothersomeness: 5-point scale (0=none, 4 a very great deal). Satisfaction: 5-point scale (0=a very great deal to 4=not at all). A priori sample size calculation of 395 patients in each group to detect a treatment difference in outcomes at the 5% significance level, with 90% power (assuming a responder rate of 30% in the placebo group and 42% in one of the tegaserod groups).
Allocation concealment	A – Adequate

Study	**Kamm 2005**
Methods	Randomised double-blind placebo-controlled parallel group 128-centre study. Duration 14 weeks (2 weeks treatment-free baseline, 12 weeks DB treatment).

Characteristics of included studies (*Continued*)

Participants	M/F >= 18 years (86% F). Mean age 46 years. Constipation for 6 months or more, mean 15 years (defined as an average of less than three complete spontaneous bowel movements per week, together with at least one of the following symptoms occurring at least 25% of the time: straining, incomplete evacuation, very hard and/or hard stools). Exclusion criteria: Constipation caused by a known disease of the colon or pelvic floor dysfunction; metabolic disorders, neurological disorders, or other significant disease that may have prevented patients from completing the study, use of medications that affect GI function, history of laxative abuse, medical history of previously diagnosed C-IBS.
Interventions	Tegaserod 4mg (n=417) Tegaserod 12mg (n=431) Placebo (n=416)
Outcomes	Complete spontaneous bowel movements (responder rate). Weekly number of bowel movements (including complete spontaneous, and spontaneous). Time to first complete spontaneous bowel movement. Stool form. Change in other symptoms (sensation of complete evacuation, straining, bothersomeness), satisfaction, laxative use.
Notes	Responders were defined as those with a mean increase of one or more complete spontaneous bowel movements per week compared with the baseline period. Stool form assessed using the Bristol Stool Form chart (0=separate hard lumps, 7=watery, unformed stools). Straining: 0=none, 2=too much. Bothersomeness: 0=none, 4 a very great deal. Satisfaction: 0=a very great deal to 4=not at all. A priori sample size calculation of 395 patients in each group to detect a treatment difference in outcomes at the 5% significance level, with 90% power (assuming a responder rate of 30% in the placebo group and 42% in one of the tegaserod groups).
Allocation concealment	A – Adequate

Study	**Kellow 2003**
Methods	Randomised double-blind placebo-controlled parallel group 57-centre study. Duration: 18 weeks (2 treatment-free baseline, 12 DB treatment, 4 withdrawal)
Participants	M/F >= 18 years (88.1% F). Mean age (SD) in years; 35.9 (12.4) T12mg, 36.0 (12.4) Plac. IBS (Rome II criteria). Duration of IBS (mean, SD, in months); 86.3 (77.0) T12mg, 96.5 (96.8) Plac. Exclusion criteria: D-IBS; history of organic disease of GI tract; drugs affecting GI motility and/or perception; disease affecting bowel motility or likely to compromise a patient's ability to complete the study.
Interventions	Tegaserod 12mg (n=259) Placebo (n=261) Other permitted treatments: rescue laxatives or antidiarrhoeals
Outcomes	Satisfactory relief from IBS symptoms during first four weeks of DB treatment (responder rate). Satisfactory relief during weeks 1-12 of DB treatment. GI symptoms: abdominal pain/discomfort, bloating, stool frequency, stool consistency, urgency, straining, sensation of complete evacuation.
Notes	Individual symptoms assessed according to mean change from baseline in the number of days with that symptom, normalised to a 28 day interval (last 28 days of treatment). A priori sample size calculation of 173 patients per group to detect a 12.5% difference in SGA of Relief responder rates with 80% power, assuming a 32.5% placebo response.

Allocation concealment	B – Unclear

Study	**Khoshoo 2006**
Methods	Randomised open controlled parallel group study. Duration: 4 weeks treatment
Participants	M/F 13-18 years (60% F). Mean age (SD) 15 years. C-IBS (Rome II criteria). Duration of IBS (mean in months, SD) 7.38 (2.27) T12mg + laxative, 6.93 (2.27) laxative. Exclusion criteria: underlying illness or taking any concomitant drugs.
Interventions	Tegaserod 12mg + polyethylene glycol 17g (n=21) Polyethylene glycol 17g (n=27)
Outcomes	Abdominal pain. Bowel movements.
Notes	Abdominal pain measured on a scale of 0-10, none-worse possible. a priori sample size calculation of 21 patients in each group to detect a 50% difference in outcomes at the 5% significance level, with 90% power. Prior to initiation of study medication, all patients underwent a bowel 'cleanout'.
Allocation concealment	D – Not used

Study	**Lefkowitz 1999a**
Methods	Randomised double-blind placebo-controlled parallel group dose-ranging 45-centre study. Duration 16 weeks (4 baseline, 12 DB treatment)
Participants	M/F >= 18 years. C-IBS (Rome I criteria).
Interventions	Tegaserod 1mg (n=?) Tegaserod 4mg (n=?) Tegaserod 12mg (n=?) Tegaserod 24mg (n=?) Placebo (n=?) Total n=547
Outcomes	SGA of GI symptoms. Abdominal discomfort. Quality of life (SF-36). SGA of constipation.
Notes	Responder rates determined for each SGA. Abstract publication of study only. No details of statistical or other analyses used.
Allocation concealment	D – Not used

Study	**Lefkowitz 1999b**
Methods	Randomised double-blind placebo-controlled parallel group 49-centre study. Duration: 16 weeks (4 baseline, 12 DB treatment)
Participants	M/F >=12 years (87% F). Mean age (SD) 43 (13) years. C-IBS (Rome I criteria). Minimum of 3 months symptoms. Duration of IBS (mean in months, SD) 175 (158).

Characteristics of included studies (*Continued*)

Interventions	Tegaserod 4mg (n=265) Tegaserod 12mg (267) Placebo (n=267) Other permitted treatments: laxatives for severe constipation; chronic stable doses of bulking agents or antidepressants.
Outcomes	SGA of Relief. Abdominal pain and discomfort. Bowel habit. Number of bowel movements. Bloating.
Notes	Abdominal pain, and bloating assessed on a 6-point ordinal scale. Stool consistency assessed on a 7-point scale. Abstract publication of study only.
Allocation concealment	D – Not used

Study	**Muller-Lissner 2001**
Methods	Randomised double-blind placebo-controlled parallel group 92-centre study. Duration: 16 weeks (4 treatment-free baseline, 12 DB treatment)
Participants	M/F >= 18 years (83% F). Mean age (SD) in years; 45.6 (13.6) T12mg, 45.7 (14.4) T4mg, 46.1 (13.6) Plac. C-IBS (Rome I criteria, 88.5% met Rome II criteria). Minimum of 3 months symptoms. Duration of IBS (median, in years); 10.0 T12mg & T4mg, 8.2 Plac. Organic disease excluded. Exclusion criteria: history of diarrhoea; drugs affecting GI motility and/or perception; conditions affecting gastric or bowel transit.
Interventions	Tegaserod 4mg (n=299) Tegaserod 12mg (n=294) Placebo (n=288) Other permitted treatments: laxatives for severe constipation; loperamide for diarrhoea; chronic stable doses of bulking agents or antidepressants
Outcomes	SGA of Relief (responder rate). Abdominal pain and discomfort. Bowel habit. Bloating. Bowel movements.
Notes	Abdominal pain and discomfort assessed using 100mm VAS. Stool consistency assessed using 7-point ordinal scale. A priori sample size calculation of 231 patients per group to detect a 15% difference in SGA of Relief responder rates with 80% power, assuming a 30% placebo response.
Allocation concealment	B – Unclear

Study	**Novick 2002**
Methods	Randomised double-blind placebo-controlled parallel group 131-centre study. Duration: 20 weeks (4 treatment-free baseline, 12 DB treatment, 4 withdrawal).
Participants	F >= 18 years. Mean age (SD) in years; 41.5 (10.8) T12mg, 41.0 (11.7) Plac. C-IBS (Rome I criteria). Minimum of 3 months symptoms. Duration of IBS (mean, SD, in years); 16.0 (12.2) T12mg, 16.3 (12.9) Plac.

	Organic disease excluded. Exclusion criteria: Significant diarrhoea; drugs affecting GI motility and/or perception; GI anatomy or conditions that affect bowel transit; cathartic colon.
Interventions	Tegaserod 12mg (n=767) Placebo (n=752) Other permitted treatments: chronic stable treatment with fibre or bulking agents. Prohibited; non-bulking laxatives
Outcomes	SGA of Relief (responder rate). Abdominal pain and discomfort. Bowel habit. Satisfaction with bowel habit. GI symptoms.
Notes	Mean score difference of abdominal pain and discomfort, and of bowel habit reported. Stool consistency, and bloating assessed using a 7-point ordinal scale. Responder for Satisfaction with bowel habit if very or somewhat satisfied at 50% of assessments. More patients in the T group used laxatives than the Plac group, p<0.05. A priori sample size calculation of 764 patients per group to detect a 8% difference in SGA of Relief responder rates with 90% power, assuming a 33% placebo response.
Allocation concealment	B – Unclear

Study	**Nyhlin 2004**
Methods	Randomised double-blind placebo-controlled parallel group 91-centre study. Duration: 18 weeks (2 treatment-free baseline, 12 DB treatment, 4 withdrawal).
Participants	M/F 18-65 years (86% F). Mean age (SD) in years; 44.6 (12) T12mg, 44.0 (12.1) Plac. C-IBS (Rome II criteria). Duration of IBS (mean, in years); 17.4 T12mg, 16.6 Plac. Exclusion criteria: D-IBS, drugs affecting GI motility and/or perception; mean abdominal pain/discomfort score of 1 or less on a 5-point scale where 1=mild, severe laxative dependence.
Interventions	Tegaserod 12mg (n=327) Placebo (n=320)
Outcomes	Satisfactory relief from IBS symptoms during first four weeks of DB treatment (responder rate). Satisfactory relief during weeks 1-12 of DB treatment. GI symptoms: abdominal pain/discomfort, bloating, stool frequency, stool consistency, urgency, straining, sensation of complete evacuation.
Notes	Individual symptoms assessed according to mean change from baseline in the number of days with that symptom, normalised to a 28 day interval (last 28 days of treatment). A priori sample size calculation of 255 patients per group to detect a 12% difference in SGA of Relief responder rates with 90% power, assuming a 33% placebo response.
Allocation concealment	B – Unclear

Study	**Reilly 2005**
Methods	See Tack 2005.
Participants	63% of women from the Tack 2005 study who were employed.
Interventions	First treatment period: Tegaserod 12mg (n=1363) Placebo (n=312)

Outcomes	Work Productivity and Activity Impairment (WPAI)
Notes	The validated WPAI:IBS was modified to make it appropriate to patients with constipation (diarrhoea was eliminated from the description of IBS symptoms in the introduction). The questionnaire was self-administered. Only data for this outcome for the first treatment period were reported.
Allocation concealment	A – Adequate

Study	**Tack 2005**
Methods	Randomised double-blind placebo-controlled parallel group 267-centre study. Duration: up to 22 weeks (2-week treatment-free baseline, 4-weeks DB treatment, 2-12 week treatment-free interval, 4 weeks repeated treatment).
Participants	F >= 18 years. Mean age in years; 41.9 T12mg, 42.6 Plac. C-IBS (Rome II criteria). Duration of IBS (mean, in years); 13.1 T12mg, 13.4 Plac. Exclusion criteria: Diarrhoea at least 25% of the time during the previous 3 months, history of cathartic colon or laxative abuse, or any other significant bowel disorders.
Interventions	First treatment period: Tegaserod 12mg (n=2135) Placebo (n=525). Second treatment period: Tegaserod 12mg (n=488) Placebo (n=495).
Outcomes	Satisfactory relief from IBS symptoms; abdominal discomfort/pain. Relief of constipation. Improvement in abdominal discomfort/pain, bloating, mean stool consistency. Overall satisfaction with treatment. Quality of life. Work Productivity and Activity Impairment (WPAI:IBS - reported in Reilly 2005)
Notes	Patients with at least partial response (satisfactory relief of either overall IBS symptoms for at least 2 of 4 weeks treatment or abdominal pain/discomfort in at least 2 of the 4 weeks) entered the treatment free interval. Patients were eligible for repeated treatment if symptoms recurred within 12 weeks (absence of satisfactory relief of overall IBS symptoms for at least 3 of 4 consecutive weeks and abdominal pain/discomfort for at least 3 of 4 consecutive weeks). Data available for the first tegaserod treatment period only. The validated WPAI:IBS was modified to make it appropriate to patients with constipation (diarrhoea was eliminated from the description of IBS symptoms in the introduction). The questionnaire was self-administered. A priori sample size calculation for the first treatment period of 2000 tegaserod and 500 placebo to detect a 15% difference in responder rates for overall relief of GI symptoms, and 10% for relief of abdominal discomfort/pain during first and repeated treatment simultaneously with 90% power at a two-sided significance level of 5%.
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	**Reason for exclusion**
Appel-Dingemanse	No clinical endpoints, purely a pharmacokinetic study. Comparator arm not appropriate (healthy volunteers).

Characteristics of excluded studies (*Continued*)

Bardhan 2004	In this study all patients received tegaserod, with responders then randomised to continue or to withdraw tegaserod treatment. There was no control group. The study was also open label.
Prather 2000	No clinical endpoints.
Tougas 2002	Not a randomised controlled trial. All patients received tegaserod treatment.

ADDITIONAL TABLES

Table 01. SGA of Relief responder rates

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
B307	42.2%	38.3%	37.0%	Applies to last 4 weeks of DB treatment. In the 12 mg group, patients started on 4 mg for one month, which could be increased to 12 mg according to response (65% of patients took 12 mg after the first month). The responder rate is adjusted for missing SGAs, laxative use, and duration of treatment. P = 0.142 for 12 mg vs placebo, P = 0.837 for 4 mg vs placebo
Kellow 2003	46.8%	No 4 mg group	28.3%	Applies to weeks 1 to 4 of DB treatment. P < 0.0001 for 12 mg vs placebo
Lefkowitz 1999b	45.7%	38.9%	33.3%	Applies to last 4 weeks of DB treatment. The responder rate is adjusted for missing SGAs, laxative use, and duration of treatment. P = 0.004 for 12 mg vs placebo, P = 0.157 for 4 mg vs placebo
Muller-Lissner 2001	38.4%	38.8%	30.2%	Applies to last 4 weeks of DB treatment. The responder rate is adjusted for missing SGAs, laxative use, and duration of treatment. P = 0.033 for 12 mg vs placebo, P = 0.018 for 4 mg vs placebo
Novick 2002	43.5%	No 4 mg group	38.8%	Applies to last 4 weeks of DB treatment. The responder rate is adjusted for missing SGAs, laxative use, and duration of treatment. P < 0.033 for 12 mg vs placebo
Hamling 1998	No numerical data	No numerical data	No numerical data	Responder rates reported in abstract but not for ITT population, or for each tegaserod dosage group
Lefkowitz 1999a	No numerical data	No numerical data	No numerical data	
Nyhlin 2004	30.5%	No 4 mg group	20.8%	Applies to weeks 1 to 4 of DB treatment. P = 0.006 for 12 mg vs placebo
Nyhlin 2004	31%	No 4 mg group	20.4%	Applies to weeks 1 to 12 of DB treatment. P = 0.0027 for 12 mg vs placebo
Tack 2005	33.7%	No 4 mg group	24.2%	Applies to weeks 1 to 4 of DB treatment. Difference in response rate 9.3%, 95% CI 5.3 to 13.3), P < 0.0001

Table 02. Abdominal pain and discomfort responder rates

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
B307	27.6%	25.5%	30.6%	In the 12 mg group, patients started on 4 mg for one month, which could be increased to 12 mg according to response (65% of patients took 12 mg after the first month). P = 0.411 for 12 mg vs placebo, P = 0.141 for 4 mg vs placebo
Hamling 1998	No numerical data	No numerical data	No numerical data	Responder rates reported in abstract but not for ITT population, or for each tegaserod dosage group
Lefkowitz 1999a	No numerical data	No numerical data	No numerical data	
Lefkowitz 1999b	25.1%	23.4%	18.7%	P = 0.075 for 12 mg vs placebo, P = 0.185 for 4 mg vs placebo
Muller-Lissner 2001	29.9%	29.8%	22.6%	P = 0.044 for 12 mg vs placebo, P = 0.055 for 4 mg vs placebo
Novick 2002	No responder rate	No 4mg group	No responder rate	Mean score differences reported on 7-point scale (endpoint minus baseline); -1.01 for 12 mg, -0.80 for placebo, P < 0.003

Table 03. Bowel habit responder rates

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
B307	24.0%	27.0%	25.0%	In the 12 mg group, patients started on 4 mg for one month, which could be increased to 12 mg according to response (65% took 12mg after the first month). P = 0.847 for 12 mg vs placebo, P = 0.661 for 4 mg vs placebo
Lefkowitz 1999b	24.7%	26.4%	20.2%	P = 0.218 for 12 mg vs placebo, P = 0.082 for 4 mg vs placebo
Muller-Lissner 2001	26.2%	28.8%	22.6%	P = 0.337 for 12 mg vs placebo, P = 0.096 for 4 mg vs placebo
Novick 2002	No responder rate	No 4 mg group	No responder rate	Mean score difference (endpoint minus baseline) reported, on a 7-point ordinal scale; -1.30 for 12 mg, -0.95 for placebo, P < 0.001

Table 04. Satisfaction with bowel habit response rates

Novick 2002	Month 1	Month 2	Month 3
Tegaserod 12 mg	56.0%	58.7%	60.4%
Placebo	41.1%	50.1%	52.7%
P for tegaserod vs placebo	P < 0.001	P = 0.002	P = 0.007

Table 05. Diarrhoea (adverse effect)

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
Fidelholtz 2002	17.6%	48.6%	35.3%	Study included D-IBS patients. P = NS between groups
Kellow 2003	10.0%	No 4 mg group	3.1%	Study included C-IBS patients. P value not reported
Muller-Lissner 2001	9.6%	7.1%	2.5%	Study included C-IBS patients. P value not reported
Novick 2002	6.4%	No 4 mg group	2.9%	Study included C-IBS patients. P value not reported
Nyhlin 2004	9.2%	No 4 mg group	1.3%	Study included C-IBS patients. P value not reported
Kamm 2005	5.8%	3.9%	2.2%	Study included patients with chronic constipation. P = 0.1516 for 4 mg vs placebo, P = 0.0072 for 12 mg vs placebo
Johanson 2004	7.3%	4.5%	3.8%	Study included C-IBS patients. P value not reported

Table 06. Headache (adverse effect)

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
Fidelholtz 2002	20.6%	28.6%	23.5%	P = NS
Kellow 2003	12.0%	No 4 mg group	11.1%	P value not reported
Muller-Lissner 2001	27.3%	30.6%	27.3%	P value not reported
Novick 2002	9.0%	No 4 mg group	5.7%	P value not reported
Nyhlin 2004	8.0%	No 4 mg group	4.7%	P value not reported
Kamm 2005	12.3%	11.1%	13.7%	P value not reported
Johanson 2004	9.8%	9.2%	12.8%	P value not reported

Table 07. Abdominal pain (adverse effect)

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
Fidelholtz 2002	20.6%	31.4%	23.5%	P = NS
Kellow 2003	5.8%	No 4 mg group	3.1%	P value not reported
Muller-Lissner 2001	16.7%	16.5%	17.1%	P value not reported
Novick 2002	6.4%	No 4 mg group	5.7%	P value not reported
Nyhlin 2004	4.9%	No 4 mg group	3.8%	P value not reported

Table 08. Nausea (adverse effect)

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
Kellow 2003	4.2%	No 4 mg group	3.4%	P value not reported
Muller-Lissner 2001	7.2%	7.4%	8.7%	P value not reported

Table 08. Nausea (adverse effect) (*Continued*)

Study	Tegaserod 12 mg	Tegaserod 4 mg	Placebo	Comments
Novick 2002	6.8%	No 4 mg group	4.7%	P value not reported
Nyhlin 2004	5.5%	No 4 mg group	5.1%	P value not reported

Table 09. Abdominal pain

Study	Outcome	Teg 12 mg + laxative	Laxative	Comments
Khoshoo 2006	Mean pain score at 4 weeks	4.29 (SD 2.31)	6.15 (SD 2.38)	Scored on a scale of 0 to 10. P < 0.05 between groups
Khosoo 2006	% with good pain reduction (3 or more points on scale)	66.7%	18.5%	P < 0.05 between groups
Khosoo 2006	% with no pain reduction (2 points or less on pain scale)	23.8%	59.3%	P < 0.05 between groups
Khosoo 2006	% with increased pain (not defined)	9.5%	22.2%	P < 0.05 between groups

Table 10. Responder rate for complete spontaneous bowel movements

Study	Week assessed	Tegaserod 4 mg	Tegaserod 12 mg	Placebo	Comments
Kamm 2005	4	35.6%	40.2%	26.7%	P < 0.0001 for 12 mg vs placebo, P = 0.059 for 4 mg vs placebo
Kamm 2005	12	no numerical data	43.2%	30.6%	P < 0.0001 for 12 mg vs placebo, P = 0.14 for 4 mg vs placebo
Johanson 2004	4	41.4%	43.2%	25.1%	P < 0.0001 for 12 mg vs placebo, P < 0.0001 for 4 mg vs placebo
Johanson 2004	12	40.3%	44.8%	26.9%	P < 0.0001 for 12 mg vs placebo, P < 0.0001 for 4 mg vs placebo

Table 11. Time to first bowel movement (median)

Study	Tegaserod 4 mg	Tegaserod 12 mg	Placebo	Comments
Kamm 2005	174.3	98	286.3	Hours to CSBM. P < 0.007 for 4 mg and 12 mg vs placebo
Johanson 2004	117	73	229	Hours to CSBM. P < 0.01 for 4 mg and P < 0.001 for 12 mg vs placebo
Kamm 2005	21.3	18.4	37.2	Hours to SBM. P < 0.001 for 4 mg and 12 mg vs placebo
Johanson 2004	data shown in graph only	data shown in graph only	data shown in graph only	

Table 12. Outcomes of repeated tegaserod treatment (Tack 2005)

Outcome	Tegaserod 12mg	Placebo	Comments
Satisfactory relief of overall IBS symptoms (75% of the time)	44.9%	28.7%	(difference in response rate 16.6%, 95% CI 10.5 to 22.2), P < 0.0001
Satisfactory relief of abdominal pain and discomfort (75% of the time)	42.4%	27.1%	(difference in response rate 15.9%, 95% CI 10.3 to 21.5), P < 0.0001
Satisfactory relief of constipation (75% of the time)	45.1%	27.5%	P < 0.0001
Improvement in abdominal pain and discomfort	54.2%	41.8%	P < 0.0001 (1-point or greater improvement on 7-point scale)

ANALYSES

Comparison 01. Tegaserod 12mg vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 SGA of Relief at endpoint	4	3194	Relative Risk (Fixed) 95% CI	1.19 [1.09, 1.29]
02 Abdominal pain and discomfort at endpoint	3	1675	Relative Risk (Random) 95% CI	1.16 [0.89, 1.51]
03 SGA of relief at endpoint (fully published studies only)	2	2101	Relative Risk (Fixed) 95% CI	1.16 [1.04, 1.29]
04 Bowel habit	3	1675	Relative Risk (Fixed) 95% CI	1.10 [0.93, 1.31]
05 Diarrhoea	6	5010	Relative Risk (Fixed) 95% CI	2.80 [2.13, 3.68]
06 Headache	6	5010	Relative Risk (Fixed) 95% CI	1.07 [0.92, 1.24]
07 Abdominal pain	5	4112	Relative Risk (Fixed) 95% CI	1.03 [0.83, 1.28]
08 Nausea	5	4112	Relative Risk (Fixed) 95% CI	1.21 [0.93, 1.57]
09 Complete spontaneous bowel movement responders at week 12	2	1745	Relative Risk (Fixed) 95% CI	1.54 [1.35, 1.75]
10 Weekly frequency of bowel movements	6	5154	Weighted Mean Difference (Fixed) 95% CI	0.69 [0.55, 0.83]
11 SGA of relief weeks 1-4 of DB treatment	2	3180	Relative Risk (Fixed) 95% CI	1.46 [1.28, 1.66]

Comparison 02. Tegaserod 4mg vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 SGA of Relief at endpoint	3	1685	Relative Risk (Fixed) 95% CI	1.15 [1.02, 1.31]
02 Abdominal pain and discomfort at endpoint	3	1685	Relative Risk (Random) 95% CI	1.10 [0.82, 1.49]
03 Bowel habit	3	1685	Relative Risk (Fixed) 95% CI	1.21 [1.03, 1.43]
04 Weekly frequency of bowel movements	6	5103	Weighted Mean Difference (Fixed) 95% CI	0.52 [0.38, 0.66]
05 Diarrhoea	3	2317	Relative Risk (Fixed) 95% CI	1.70 [1.12, 2.59]

Comparison 03. Tegaserod 12mg vs 4mg

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 SGA of Relief at endpoint	3	1682	Relative Risk (Fixed) 95% CI	1.09 [0.97, 1.22]
02 Abdominal pain and discomfort at endpoint	3	1682	Relative Risk (Fixed) 95% CI	1.05 [0.90, 1.23]
03 Bowel habit	3	1682	Relative Risk (Fixed) 95% CI	0.91 [0.78, 1.07]
04 Weekly frequency of bowel movements	6	5175	Weighted Mean Difference (Fixed) 95% CI	0.17 [0.02, 0.32]

Comparison 04. Tegaserod 4mg & 12mg vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 SGA of Relief at endpoint	4	4040	Relative Risk (Fixed) 95% CI	1.17 [1.08, 1.27]
02 Abdominal pain and discomfort at endpoint	3	2521	Relative Risk (Random) 95% CI	1.13 [0.85, 1.51]
03 Bowel habit	3	2521	Relative Risk (Fixed) 95% CI	1.16 [1.00, 1.34]

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Chronic Disease; Constipation [*drug therapy]; Gastrointestinal Agents [*therapeutic use]; Indoles [*therapeutic use]; Irritable Bowel Syndrome [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans

COVER SHEET

Title Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Authors Evans BW, Clark WK, Moore DJ, Whorwell PJ

Contribution of author(s) BWE led and co-ordinated the review, prepared the protocol, undertook the searches for and reviewed the data on effectiveness (independently assessing its quality and extracting data) and prepared the final report.
WKC independently reviewed the effectiveness data, assessed its quality and extracted data, and provided advice on the protocol and final report.
DJM provided methodological advice and steer, and acted as third opinion in the event of disagreement between BWE and WKC. DJM also provided advice on the protocol and final report.
PJW provided clinical advice on the protocol and final report, and helped with ad hoc clinical enquiries.

Issue protocol first published 2003/1

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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	22 May 2007
Date new studies found and included/excluded	22 May 2007
Date authors' conclusions section amended	27 May 2007
Contact address	Beti Evans School of Pharmacy University of Hertfordshire College Lane Campus Hatfield AL10 9AB UK E-mail: b.w.evans@herts.ac.uk Tel: 44 170 728 1052
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Tegaserod 12mg vs placebo, Outcome 01 SGA of Relief at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 01 SGA of Relief at endpoint

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	116/275	105/284		18.0	1.14 [0.93, 1.40]
Lefkowitz 1999b	122/267	89/267		15.5	1.37 [1.11, 1.70]
Muller-Lissner 2001	113/294	87/288		15.3	1.27 [1.01, 1.60]
Novick 2002	334/767	292/752		51.3	1.12 [0.99, 1.27]
Total (95% CI)	1603	1591		100.0	1.19 [1.09, 1.29]

Total events: 685 (Tegaserod 12mg), 573 (Placebo)

Test for heterogeneity chi-square=3.09 df=3 p=0.38 I^2 =2.8%

Test for overall effect z=3.88 p=0.0001

Analysis 01.02. Comparison 01 Tegaserod 12mg vs placebo, Outcome 02 Abdominal pain and discomfort at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 02 Abdominal pain and discomfort at endpoint

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
B307	76/275	87/284		35.8	0.90 [0.70, 1.17]
Lefkowitz 1999b	67/267	50/267		30.0	1.34 [0.97, 1.85]
Muller-Lissner 2001	88/294	65/288		34.2	1.33 [1.01, 1.75]
Total (95% CI)	836	839		100.0	1.16 [0.89, 1.51]

Total events: 231 (Tegaserod 12mg), 202 (Placebo)

Test for heterogeneity chi-square=5.24 df=2 p=0.07 I^2 =61.8%

Test for overall effect z=1.08 p=0.3

Analysis 01.03. Comparison 01 Tegaserod 12mg vs placebo, Outcome 03 SGA of relief at endpoint (fully published studies only)

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 03 SGA of relief at endpoint (fully published studies only)

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Muller-Lissner 2001	113/294	87/288		23.0	1.27 [1.01, 1.60]
Novick 2002	334/767	292/752		77.0	1.12 [0.99, 1.27]
Total (95% CI)	1061	1040		100.0	1.16 [1.04, 1.29]

Total events: 447 (Tegaserod 12mg), 379 (Placebo)

Test for heterogeneity chi-square=0.93 df=1 p=0.34 I^2 =0.0%

Test for overall effect z=2.67 p=0.008

Analysis 01.04. Comparison 01 Tegaserod 12mg vs placebo, Outcome 04 Bowel habit

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 04 Bowel habit

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	66/275	71/284		36.9	0.96 [0.72, 1.28]
Lefkowitz 1999b	66/267	54/267		28.5	1.22 [0.89, 1.68]
Muller-Lissner 2001	77/294	65/288		34.6	1.16 [0.87, 1.55]
Total (95% CI)	836	839		100.0	1.10 [0.93, 1.31]

Total events: 209 (Tegaserod 12mg), 190 (Placebo)

Test for heterogeneity chi-square=1.40 df=2 p=0.50 I^2 =0.0%

Test for overall effect z=1.13 p=0.3

Analysis 01.05. Comparison 01 Tegaserod 12mg vs placebo, Outcome 05 Diarrhoea

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

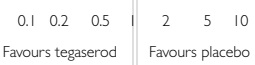
Outcome: 05 Diarrhoea

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kellow 2003	26/259	8/261		11.8	3.28 [1.51, 7.10]
Muller-Lissner 2001	28/294	7/288		10.5	3.92 [1.74, 8.83]
Novick 2002	49/767	22/752		32.9	2.18 [1.33, 3.57]
Nyhlin 2004	30/327	4/317		6.0	7.27 [2.59, 20.40]
Johanson 2004	33/451	17/447		25.3	1.92 [1.09, 3.40]
Kamm 2005	25/431	9/416		13.6	2.68 [1.27, 5.68]
Total (95% CI)	2529	2481		100.0	2.80 [2.13, 3.68]

Total events: 191 (Tegaserod 12mg), 67 (Placebo)

Test for heterogeneity chi-square=6.76 df=5 p=0.24 I^2 =26.0%

Test for overall effect z=7.40 p<0.00001



Analysis 01.06. Comparison 01 Tegaserod 12mg vs placebo, Outcome 06 Headache

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 06 Headache

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kellow 2003	31/259	29/261		10.3	1.08 [0.67, 1.73]
Muller-Lissner 2001	80/294	78/288		28.0	1.00 [0.77, 1.31]
Novick 2002	69/767	43/752		15.4	1.57 [1.09, 2.27]
Nyhlin 2004	26/327	15/317		5.4	1.68 [0.91, 3.11]
Johanson 2004	44/451	57/447		20.3	0.77 [0.53, 1.11]
Kamm 2005	53/431	57/416		20.6	0.90 [0.63, 1.27]
Total (95% CI)	2529	2481		100.0	1.07 [0.92, 1.24]

Total events: 303 (Tegaserod 12mg), 279 (Placebo)

Test for heterogeneity chi-square=10.60 df=5 p=0.06 I^2 =52.9%

Test for overall effect z=0.83 p=0.4

Analysis 01.07. Comparison 01 Tegaserod 12mg vs placebo, Outcome 07 Abdominal pain

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 07 Abdominal pain

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kellow 2003	15/259	8/261		5.5	1.89 [0.82, 4.38]
Muller-Lissner 2001	49/294	49/288		34.2	0.98 [0.68, 1.41]
Novick 2002	49/767	43/752		30.0	1.12 [0.75, 1.66]
Nyhlin 2004	16/327	12/317		8.4	1.29 [0.62, 2.69]
Kamm 2005	21/431	31/416		21.8	0.65 [0.38, 1.12]
Total (95% CI)	2078	2034		100.0	1.03 [0.83, 1.28]

Total events: 150 (Tegaserod 12mg), 143 (Placebo)

Test for heterogeneity chi-square=5.35 df=4 p=0.25 I^2 =25.2%

Test for overall effect z=0.23 p=0.8

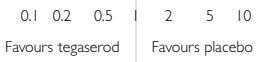
Analysis 01.08. Comparison 01 Tegaserod 12mg vs placebo, Outcome 08 Nausea

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 08 Nausea

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kellow 2003	11/259	9/261		9.1	1.23 [0.52, 2.92]
Muller-Lissner 2001	21/294	25/288		25.5	0.82 [0.47, 1.44]
Novick 2002	52/767	35/752		35.7	1.46 [0.96, 2.21]
Nyhlin 2004	18/327	16/317		16.4	1.09 [0.57, 2.10]
Kamm 2005	19/431	13/416		13.4	1.41 [0.71, 2.82]
Total (95% CI)	2078	2034		100.0	1.21 [0.93, 1.57]
Total events: 121 (Tegaserod 12mg), 98 (Placebo)					
Test for heterogeneity chi-square=2.89 df=4 p=0.58 I^2 =0.0%					
Test for overall effect z=1.43 p=0.2					



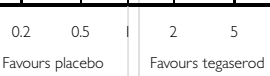
Analysis 01.09. Comparison 01 Tegaserod 12mg vs placebo, Outcome 09 Complete spontaneous bowel movement responders at week 12

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 09 Complete spontaneous bowel movement responders at week 12

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kamm 2005	186/431	127/416		51.7	1.41 [1.18, 1.69]
Johanson 2004	202/451	120/447		48.3	1.67 [1.39, 2.01]
Total (95% CI)	882	863		100.0	1.54 [1.35, 1.75]
Total events: 388 (Tegaserod 12mg), 247 (Placebo)					
Test for heterogeneity chi-square=1.58 df=1 p=0.21 I^2 =36.8%					
Test for overall effect z=6.53 p<0.00001					



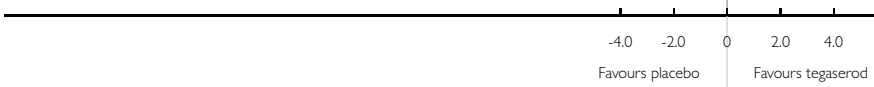
Analysis 01.10. Comparison 01 Tegaserod 12mg vs placebo, Outcome 10 Weekly frequency of bowel movements

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 10 Weekly frequency of bowel movements

Study	Tegaserod 12mg N	Mean(SD)	Placebo N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 Complete spontaneous bowel movements (CSBM)							
Johanson 2004	440	1.90 (2.10)	431	1.30 (1.70)		29.4	0.60 [0.35, 0.85]
Kamm 2005	431	1.90 (2.10)	416	1.30 (1.60)		30.0	0.60 [0.35, 0.85]
Subtotal (95% CI)	871		847			59.4	0.60 [0.42, 0.78]
Test for heterogeneity chi-square=0.0 df=1 p=1.00 I^2 =0.0%							
Test for overall effect z=6.59 p<0.00001							
02 Spontaneous bowel movements (SBM)							
Johanson 2004	440	5.40 (3.80)	431	4.60 (3.20)		8.7	0.80 [0.33, 1.27]
Kamm 2005	431	5.10 (3.30)	416	4.10 (3.20)		9.9	1.00 [0.56, 1.44]
Subtotal (95% CI)	871		847			18.5	0.91 [0.59, 1.23]
Test for heterogeneity chi-square=0.38 df=1 p=0.54 I^2 =0.0%							
Test for overall effect z=5.57 p<0.00001							
03 Bowel movements							
Johanson 2004	440	6.10 (3.50)	431	5.40 (3.00)		10.1	0.70 [0.27, 1.13]
Kamm 2005	431	5.70 (3.00)	416	4.90 (2.90)		12.0	0.80 [0.40, 1.20]
Subtotal (95% CI)	871		847			22.1	0.75 [0.46, 1.05]
Test for heterogeneity chi-square=0.11 df=1 p=0.74 I^2 =0.0%							
Test for overall effect z=5.05 p<0.00001							
Total (95% CI)	2613		2541			100.0	0.69 [0.55, 0.83]
Test for heterogeneity chi-square=3.42 df=5 p=0.64 I^2 =0.0%							
Test for overall effect z=9.85 p<0.00001							



Analysis 01.11. Comparison 01 Tegaserod 12mg vs placebo, Outcome 11 SGA of relief weeks 1-4 of DB treatment

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 01 Tegaserod 12mg vs placebo

Outcome: 11 SGA of relief weeks 1-4 of DB treatment

Study	Tegaserod 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kellow 2003	145/259	91/261		30.8	1.61 [1.32, 1.96]
Tack 2005	719/2135	127/525		69.2	1.39 [1.18, 1.64]
Total (95% CI)	2394	786		100.0	1.46 [1.28, 1.66]

Total events: 864 (Tegaserod 12mg), 218 (Placebo)

Test for heterogeneity chi-square=1.22 df=1 p=0.27 I^2 =18.3%

Test for overall effect z=5.81 p<0.00001

Analysis 02.01. Comparison 02 Tegaserod 4mg vs placebo, Outcome 01 SGA of Relief at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 02 Tegaserod 4mg vs placebo

Outcome: 01 SGA of Relief at endpoint

Study	Tegaserod 4mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	108/282	105/284		37.1	1.04 [0.84, 1.28]
Lefkowitz 1999b	103/265	89/267		31.5	1.17 [0.93, 1.46]
Muller-Lissner 2001	116/299	87/288		31.4	1.28 [1.02, 1.61]
Total (95% CI)	846	839		100.0	1.15 [1.02, 1.31]

Total events: 327 (Tegaserod 4mg), 281 (Placebo)

Test for heterogeneity chi-square=1.86 df=2 p=0.39 I^2 =0.0%

Test for overall effect z=2.21 p=0.03

Analysis 02.02. Comparison 02 Tegaserod 4mg vs placebo, Outcome 02 Abdominal pain and discomfort at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 02 Tegaserod 4mg vs placebo

Outcome: 02 Abdominal pain and discomfort at endpoint

Study	Tegaserod 4mg n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
B307	72/282	87/284		35.2	0.83 [0.64, 1.09]
Lefkowitz 1999b	62/265	50/267		30.4	1.25 [0.90, 1.74]
Muller-Lissner 2001	89/299	65/288		34.4	1.32 [1.00, 1.74]
Total (95% CI)	846	839		100.0	1.10 [0.82, 1.49]

Total events: 223 (Tegaserod 4mg), 202 (Placebo)

Test for heterogeneity chi-square=6.42 df=2 p=0.04 I^2 =68.9%

Test for overall effect z=0.65 p=0.5

Analysis 02.03. Comparison 02 Tegaserod 4mg vs placebo, Outcome 03 Bowel habit

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 02 Tegaserod 4mg vs placebo

Outcome: 03 Bowel habit

Study	Tegaserod 4mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	76/282	71/284		37.1	1.08 [0.82, 1.42]
Lefkowitz 1999b	70/265	54/267		28.2	1.31 [0.96, 1.78]
Muller-Lissner 2001	86/299	65/288		34.7	1.27 [0.96, 1.68]
Total (95% CI)	846	839		100.0	1.21 [1.02, 1.43]

Total events: 232 (Tegaserod 4mg), 190 (Placebo)

Test for heterogeneity chi-square=1.03 df=2 p=0.60 I^2 =0.0%

Test for overall effect z=2.25 p=0.02

Analysis 02.04. Comparison 02 Tegaserod 4mg vs placebo, Outcome 04 Weekly frequency of bowel movements

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 02 Tegaserod 4mg vs placebo

Outcome: 04 Weekly frequency of bowel movements

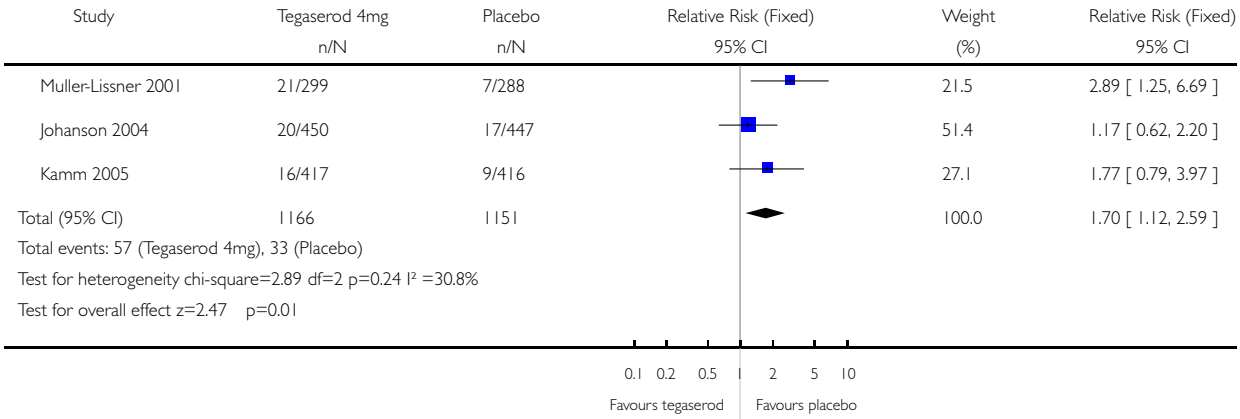
Study	Tegaserod 4mg N	Mean(SD)	Placebo N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 Complete spontaneous bowel movements (CSBM)							
Johanson 2004	437	1.90 (2.30)	431	1.30 (1.70)		26.9	0.60 [0.33, 0.87]
Kamm 2005	417	1.60 (2.00)	416	1.30 (1.60)		32.2	0.30 [0.05, 0.55]
Subtotal (95% CI)	854		847			59.1	0.44 [0.26, 0.62]
Test for heterogeneity chi-square=2.60 df=1 p=0.11 I^2 =61.6%							
Test for overall effect z=4.72 p<0.00001							
02 Spontaneous bowel movements (SBM)							
Johanson 2004	437	5.50 (4.00)	431	4.60 (3.20)		8.4	0.90 [0.42, 1.38]
Kamm 2005	417	4.70 (3.10)	416	4.10 (3.20)		10.6	0.60 [0.17, 1.03]
Subtotal (95% CI)	854		847			19.0	0.73 [0.41, 1.05]
Test for heterogeneity chi-square=0.83 df=1 p=0.36 I^2 =0.0%							
Test for overall effect z=4.49 p<0.00001							
03 Bowel movements							
Johanson 2004	437	6.20 (3.70)	431	5.40 (3.00)		9.7	0.80 [0.35, 1.25]
Kamm 2005	417	5.30 (3.00)	416	4.90 (2.90)		12.1	0.40 [0.00, 0.80]
Subtotal (95% CI)	854		847			21.8	0.58 [0.28, 0.88]
Test for heterogeneity chi-square=1.70 df=1 p=0.19 I^2 =41.2%							
Test for overall effect z=3.79 p=0.0001							
Total (95% CI)	2562		2541			100.0	0.52 [0.38, 0.66]
Test for heterogeneity chi-square=7.78 df=5 p=0.17 I^2 =35.8%							
Test for overall effect z=7.36 p<0.00001							

Analysis 02.05. Comparison 02 Tegaserod 4mg vs placebo, Outcome 05 Diarrhoea

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 02 Tegaserod 4mg vs placebo

Outcome: 05 Diarrhoea

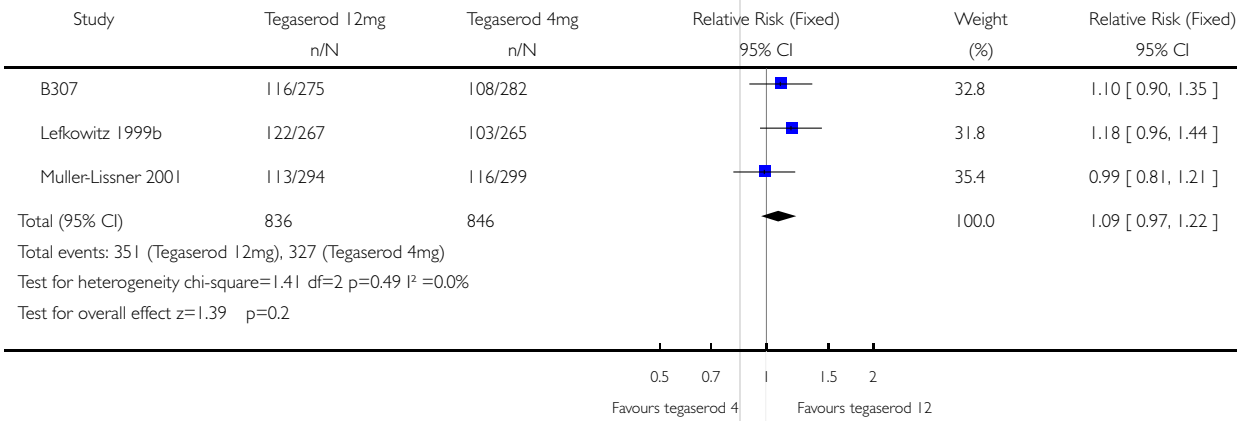


Analysis 03.01. Comparison 03 Tegaserod 12mg vs 4mg, Outcome 01 SGA of Relief at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 03 Tegaserod 12mg vs 4mg

Outcome: 01 SGA of Relief at endpoint



Analysis 03.02. Comparison 03 Tegaserod 12mg vs 4mg, Outcome 02 Abdominal pain and discomfort at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 03 Tegaserod 12mg vs 4mg

Outcome: 02 Abdominal pain and discomfort at endpoint

Study	Tegaserod 12mg n/N	Tegaserod 4mg n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	76/275	72/282		32.1	1.08 [0.82, 1.43]
Lefkowitz 1999b	67/267	62/265		28.1	1.07 [0.79, 1.45]
Muller-Lissner 2001	88/294	89/299		39.8	1.01 [0.79, 1.29]
Total (95% CI)	836	846		100.0	1.05 [0.90, 1.23]

Total events: 231 (Tegaserod 12mg), 223 (Tegaserod 4mg)

Test for heterogeneity chi-square=0.18 df=2 p=0.91 I^2 =0.0%

Test for overall effect z=0.60 p=0.6

Analysis 03.03. Comparison 03 Tegaserod 12mg vs 4mg, Outcome 03 Bowel habit

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 03 Tegaserod 12mg vs 4mg

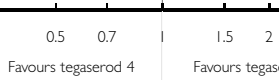
Outcome: 03 Bowel habit

Study	Tegaserod 12mg n/N	Tegaserod 4mg n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	66/275	76/282		32.5	0.89 [0.67, 1.18]
Lefkowitz 1999b	66/267	70/265		30.5	0.94 [0.70, 1.25]
Muller-Lissner 2001	77/294	86/299		37.0	0.91 [0.70, 1.18]
Total (95% CI)	836	846		100.0	0.91 [0.78, 1.07]

Total events: 209 (Tegaserod 12mg), 232 (Tegaserod 4mg)

Test for heterogeneity chi-square=0.06 df=2 p=0.97 I^2 =0.0%

Test for overall effect z=1.13 p=0.3



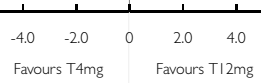
Analysis 03.04. Comparison 03 Tegaserod 12mg vs 4mg, Outcome 04 Weekly frequency of bowel movements

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 03 Tegaserod 12mg vs 4mg

Outcome: 04 Weekly frequency of bowel movements

Study	Tegaserod 12mg N	Mean(SD)	Tegaserod 4mg N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 CSBM							
Johanson 2004	440	1.90 (2.10)	437	1.90 (2.30)		26.4	0.0 [-0.29, 0.29]
Kamm 2005	431	1.90 (2.10)	417	1.60 (2.00)		29.5	0.30 [0.02, 0.58]
Subtotal (95% CI)	871		854			55.9	0.16 [-0.04, 0.36]
Test for heterogeneity chi-square=2.15 df=1 p=0.14 I^2 =53.4%							
Test for overall effect z=1.55 p=0.1							
02 SBM							
Johanson 2004	440	5.40 (3.80)	437	5.50 (4.00)		8.4	-0.10 [-0.62, 0.42]
Kamm 2005	431	5.10 (3.30)	417	4.70 (3.10)		12.1	0.40 [-0.03, 0.83]
Subtotal (95% CI)	871		854			20.5	0.19 [-0.14, 0.53]
Test for heterogeneity chi-square=2.12 df=1 p=0.15 I^2 =52.9%							
Test for overall effect z=1.15 p=0.2							
03 Bowel movements							
Johanson 2004	440	6.10 (3.50)	437	6.20 (3.70)		9.9	-0.10 [-0.58, 0.38]
Kamm 2005	431	5.70 (3.00)	417	5.30 (3.00)		13.8	0.40 [0.00, 0.80]
Subtotal (95% CI)	871		854			23.6	0.19 [-0.12, 0.50]
Test for heterogeneity chi-square=2.46 df=1 p=0.12 I^2 =59.3%							
Test for overall effect z=1.22 p=0.2							
Total (95% CI)	2613		2562			100.0	0.17 [0.02, 0.32]
Test for heterogeneity chi-square=6.78 df=5 p=0.24 I^2 =26.2%							
Test for overall effect z=2.27 p=0.02							



Analysis 04.01. Comparison 04 Tegaserod 4mg & 12mg vs placebo, Outcome 01 SGA of Relief at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 04 Tegaserod 4mg % 12mg vs placebo

Outcome: 01 SGA of Relief at endpoint

Study	Tegaserod 4mg % 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	224/557	105/284		20.8	1.09 [0.91, 1.31]
Lefkowitz 1999b	225/532	89/267		17.7	1.27 [1.04, 1.54]
Muller-Lissner 2001	229/593	87/288		17.5	1.28 [1.04, 1.57]
Novick 2002	334/767	292/752		44.0	1.12 [0.99, 1.27]
Total (95% CI)	2449	1591		100.0	1.17 [1.08, 1.27]

Total events: 1012 (Tegaserod 4mg % 12mg), 573 (Placebo)

Test for heterogeneity chi-square=2.46 df=3 p=0.48 I^2 =0.0%

Test for overall effect z=3.71 p=0.0002

Analysis 04.02. Comparison 04 Tegaserod 4mg & 12mg vs placebo, Outcome 02 Abdominal pain and discomfort at endpoint

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 04 Tegaserod 4mg % 12mg vs placebo

Outcome: 02 Abdominal pain and discomfort at endpoint

Study	Tegaserod 4mg % 12mg n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
B307	148/557	87/284		35.4	0.87 [0.69, 1.08]
Lefkowitz 1999b	129/532	50/267		30.8	1.29 [0.97, 1.73]
Muller-Lissner 2001	177/593	65/288		33.8	1.32 [1.03, 1.69]
Total (95% CI)	1682	839		100.0	1.13 [0.85, 1.51]

Total events: 454 (Tegaserod 4mg % 12mg), 202 (Placebo)

Test for heterogeneity chi-square=7.75 df=2 p=0.02 I^2 =74.2%

Test for overall effect z=0.84 p=0.4

Analysis 04.03. Comparison 04 Tegaserod 4mg & 12mg vs placebo, Outcome 03 Bowel habit

Review: Tegaserod for the treatment of irritable bowel syndrome and chronic constipation

Comparison: 04 Tegaserod 4mg % 12mg vs placebo

Outcome: 03 Bowel habit

Study	Tegaserod 4mg % 12mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
B307	142/557	71/284		37.1	1.02 [0.80, 1.30]
Lefkowitz 1999b	136/532	54/267		28.4	1.26 [0.96, 1.67]
Muller-Lissner 2001	163/593	65/288		34.5	1.22 [0.95, 1.56]
Total (95% CI)	1682	839		100.0	1.16 [1.00, 1.34]
Total events: 441 (Tegaserod 4mg % 12mg), 190 (Placebo)					
Test for heterogeneity chi-square=1.56 df=2 p=0.46 I^2 =0.0%					
Test for overall effect z=1.93 p=0.05