

Drug Class Review on Constipation Drugs

Update #1: Preliminary Scan Report #2

August 2009

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. RTI-UNC Evidence-based Practice Center does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Original Report

September 2007 (searches through April 2007)

Date of Last Scan

August 2008

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the general effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome? Given general effectiveness, what is the comparative effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome?
2. Does treatment duration influence the effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome? When should treatments be switched in patients not responding to a given drug?
3. What is the comparative tolerability and safety of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome?
4. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities, including Irritable Bowel Syndrome, for which one symptomatic treatment is more effective or associated with fewer adverse events?

Inclusion criteria**Populations**

- Adults and children with chronic constipation
- Adults and children with chronic constipation associated with Irritable Bowel Syndrome (IBS-C)

Interventions

Seven different treatments in 5 different classes are being evaluated:

5-HT4 serotonin receptor agonist

- Tegaserod maleate (Zelnorm)

Bulking agents

- Psyllium/ispaghula (Metamucil, Fiberall, Genfiber, Natural Psyllium Fiber, Hydrocil, Konsyl, Reguloid, Natural Fiber Laxative, Syllact, Seruntan)

Chloride channel activator

- Lubiprostone (Amitiza)

Osmotic laxatives

- Polyethylene glycol 3350 (Glycolax, MiraLax, Generic)
- Lactulose (Chronulac, Generic)

Stool softeners

- Docusate sodium (Ex-lax, Dioctyn, Colace, D-S-S, Dulcolax, Silace, Stool softener, Regulan SS, Genasoft, Sof-lax, Diocto, Docu, D.O.S., Generic)
- Docusate calcium (Stool softener, Sulfolax, Surfak Liquigels, DC Softgels, Generic)

Effectiveness outcomes

- General subjective measures (e.g., overall relief of GI symptoms, symptom composite score)
- Specific GI symptom/s (e.g., straining, bloating, abdominal discomfort/pain, ease of defecation, complete spontaneous bowel movement)
- Physiologic measure/s (e.g., increase in frequency of bowel movements, stool consistency)
- General well being and or QOL
- Time to effectiveness
- Switching in patients not responding to a drug
- Influence of treatment duration on the effectiveness of drugs

Safety outcomes

- Overall adverse events
- Withdrawals because of adverse events
- Specific adverse events (e.g., electrolyte abnormalities, diarrhea, bloating, nausea, flatulence, dehydration, hypovolemia)
- Serious adverse events (e.g., hepatotoxicity)

Study design

- RCTs only
- No minimum sample size
- No minimum study duration

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from April, 2007 through August 24, 2009 using terms for included drugs and indications, and limits for humans, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X.02) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 80 new citations. Of those, there are 14 new potentially relevant studies (Appendix A).

Summary of those RCTs: number of studies for each comparison

Tegaserod vs PEG 3350: 1

Tegaserod vs. placebo: 5

Lubiprostone vs. placebo: 4

PEG 3350 vs. placebo: 4

New Drugs

Methylnaltrexone bromide (Relistor) subcutaneous injection for the treatment of for opioid-induced constipation in patients with advanced illness receiving palliative care, when response to laxative therapy has not been sufficient. This indication does not meet the current eligibility criteria of our review (patients with chronic constipation or IBS-C); however, we mention it here because two PO's notified us of this new drug.

Under study for IBS-C: prucalopride (not FDA approved)

PubMed search for prucalopride (limited to controlled trials or RCTs conducted in humans) on August 27, 2009 yielded 11 citations, 7 of which described RCTs on patients with chronic constipation or IBS-C (Appendix B).

New Indications

Lubiprostone (Amitiza) has FDA approval for the treatment of irritable bowel syndrome with constipation (IBS-C) in women ≥ 18 years old (April, 2008).

New Safety Alerts***FDA:*****Lubiprostone (Amitiza)**

Recent major changes in lubiprostone label (April, 2008) include the following addition under Warnings and Precautions: patients taking lubiprostone (Amitiza) may experience dyspnea within an hour of first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing. In clinical trials conducted to study Amitiza in treatment of chronic idiopathic constipation and IBS-C there were reports of dyspnea. This was reported at 2.5% of the treated chronic idiopathic constipation population and at 0.4% in the treated IBS-C population. Although not classified as serious adverse events, some patients discontinued treatment on study because of this event. There have been postmarketing reports of dyspnea when using Amitiza 24 mcg. Most have not been characterized as serious adverse events, but some patients have discontinued therapy because of dyspnea. These events have usually been described as a sensation of chest tightness and difficulty taking in a breath, and generally have an acute onset within 30-60 minutes after taking the first dose. They generally resolve within a few hours after taking the dose, but recurrence has been frequently reported with subsequent doses.

Health Canada:

None at this time.

Appendix A. Abstracts of potentially relevant new RCTs of constipation drugs

1. Bracco, A., B. Jonsson, et al. (2007). "Economic evaluation of tegaserod vs. placebo in the treatment of patients with irritable bowel syndrome: an analysis of the TENOR study." *Value Health* **10**(4): 238-46.

OBJECTIVES: Tegaserod is effective, safe, and well-tolerated in the treatment of patients with irritable bowel syndrome (IBS) with constipation. The aim of this study was to assess, from a payer perspective, the cost-effectiveness of tegaserod in the treatment of IBS patients, based on the TEgaserod in NORdic region (TENOR) trial data. **METHODS:** Female and male patients (Rome II criteria) were randomized to receive tegaserod 6 mg b.i.d. or placebo for 12 weeks. Patients (247 tegaserod; 238 placebo) completed the EuroQol EQ-5D questionnaire at baseline, Week 4, and Week 12. A 12-week economic study was undertaken to assess the incremental cost-effectiveness ratio (ICER) of tegaserod in terms of cost per quality-adjusted life-year (QALY) gained. Cost-effectiveness acceptability curves were calculated to estimate the probability of tegaserod being cost-effective at different benchmark values of cost per QALY gained. **RESULTS:** By assuming a daily drug cost to payers of Euro 2, Euro 3, and Euro 4, the ICER of tegaserod ranges between Euro 19,000 and Euro 38,000 per QALY gained, with the percentage of the bootstrap estimates below the willingness to pay level of Euro 50,000 per QALY gained ranging between 90% and 69%. **CONCLUSIONS:** This study established directly from a randomized controlled clinical trial that tegaserod is cost-effective in the treatment of non-D-IBS patients.

2. Chey, W. D., P. Pare, et al. (2008). "Tegaserod for female patients suffering from IBS with mixed bowel habits or constipation: a randomized controlled trial." *Am J Gastroenterol* **103**(5): 1217-25.

OBJECTIVES: Though the greatest proportion of irritable bowel syndrome (IBS) patients report a mixed bowel pattern (IBS-Mixed), no available therapies have been rigorously evaluated in this subgroup. This study aimed to evaluate the efficacy and safety of the 5-HT₄ agonist tegaserod in women with IBS-Mixed and IBS with constipation (IBS-C). **METHODS:** This prospective, double-blind, randomized, placebo-controlled, multicenter study was conducted in 100 centers in North America, South America, and Europe. Women with IBS-Mixed or IBS-C received tegaserod 6 mg or placebo twice daily. The primary efficacy variable was the patient's assessment of satisfactory relief over the 4-wk treatment period. The proportion of patients reporting satisfactory relief for ≥ 3 of 4 treatment weeks (75% rule) and individual IBS symptoms were assessed. **RESULTS:** In total, 661 women were randomized (IBS-Mixed 324, IBS-C 337). Baseline symptom assessments identified clear differences between the two cohorts. Tegaserod provided significant improvement in satisfactory relief of IBS symptoms over 4 wk (OR 1.75, 95% CI 1.35-2.25, $P < 0.001$) in both IBS-Mixed and IBS-C patients. Using the 75% rule, 52.3% of tegaserod-receiving IBS-M patients and 43.3% of IBS-C patients were responders (vs 36.3, OR 1.88, 95% CI 1.16-3.04, $P < 0.010$; and 28.9, OR 1.90, 95%

CI 1.19-3.05, $P < 0.008$ for placebo, respectively). The most frequent adverse events leading to study discontinuation in tegaserod-treated patients were diarrhea (1.5%) and abdominal pain (0.9%). Overall 7% of IBS-C patients reported diarrhea compared to 12% of IBS-Mixed (placebo 2.4%, 1.8%, respectively). CONCLUSIONS: Tegaserod is effective in treating overall IBS symptoms in patients with IBS-Mixed and IBS-C.

3. Di Palma, J. A., M. B. Cleveland, et al. (2007). "A comparison of polyethylene glycol laxative and placebo for relief of constipation from constipating medications." South Med J **100**(11): 1085-90.

OBJECTIVES: Medications often cause constipation and little data are available concerning treatment interventions. This study was designed to evaluate the safety and efficacy of polyethylene glycol (PEG) 3350 laxative (MiraLax) for relief of constipation from medicines associated with symptoms of constipation. METHODS: Study subjects were enrolled who met defined criteria for chronic constipation and were also taking medications that were associated with a reported side effect incidence of more than 3% constipation. Subjects were randomized into a double-blind, parallel, multicenter study where they received 17 g per day of PEG laxative or placebo for 28 days. The primary efficacy variable, "Treatment Success," was defined as relief of ROME II criteria for constipation over the last 7 days of the treatment period. Various secondary measures were also assessed. Daily bowel movement experience, patient perception of efficacy, and safety information were recorded in a diary. Laboratory testing was performed at baseline and at end of study for hematology and blood chemistry, including BUN, calcium, electrolytes, and TSH. RESULTS: One hundred patients were enrolled at 4 study centers. Successful treatment according to the primary efficacy variable was seen in 78.3% of PEG and 39.1% of placebo subjects ($P < 0.001$). Similar results were observed in a subgroup of 28 elderly subjects. Secondary measures of number of bowel movements, complete bowel movements, satisfactory bowel movements, straining at stool and stool consistency also showed statistically significant results in favor of PEG compared with placebo ($P < 0.01$) after the first week of treatment. There were no differences inpatient reported scores for gas, cramping, or bloating between PEG and placebo. No significant differences in laboratory findings or adverse events, including the gastrointestinal category, were observed. Diarrhea and flatulence occurred more frequently with PEG treatment, although they were not individually statistically different from placebo. Similar results were observed when these symptoms were analyzed for differences due to gender, race, or age. CONCLUSIONS: PEG laxative is safe and effective for use in treating constipation in patients taking constipating medications.

4. Di Palma, J. A., M. V. Cleveland, et al. (2007). "A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation." Am J Gastroenterol **102**(9): 1964-71.

OBJECTIVE: Polyethylene glycol (PEG) 3350 (MiraLax) and tegaserod (Zelnorm), a serotonin subtype 4 receptor partial agonist, are currently approved for treatment of constipation. This study was designed to compare the efficacy of each product over a 4-wk treatment

period. **METHODS:** Study patients who met defined criteria for chronic constipation were randomized in this open-labeled, parallel, multicenter study to receive the PEG laxative as a single daily dose of 17 g or tegaserod tablets 6 mg b.i.d., for 28 days. As a primary end point, treatment success was defined for each patient as relief of modified ROME criteria for constipation for 50% or more of their treatment weeks. Various secondary measures were also assessed. An interactive voice response system (IVRS) recorded patient reported daily bowel movement experience and study efficacy and safety information. **RESULTS:** A total of 237 patients were enrolled and received treatment at one of 25 centers. Successful treatment according to the primary end point was seen in 50.0% of the PEG and 30.8% of tegaserod patients ($P=0.003$). By treatment weeks 3 and 4, significantly more PEG patients were successfully treated according to primary and secondary response definitions. PEG patients experienced more bowel movements per week ($P=0.019$) and had significantly greater improvement in constipation symptoms ($P=0.016$) based on results from a validated patient self-reported questionnaire. Tegaserod patients experienced a significantly higher incidence of headaches. Otherwise, there were no significant differences in adverse events. **CONCLUSIONS:** While PEG laxative and tegaserod are safe for their intended use in chronic constipation, PEG had superior efficacy, caused fewer headaches, and produced greater improvement of constipation symptoms.

5. Di Palma, J. A., M. V. Cleveland, et al. (2007). "A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation." Am J Gastroenterol **102**(7): 1436-41.

OBJECTIVES: Polyethylene glycol (PEG) 3350 (MiraLAX) is currently approved for the short-term treatment of occasional constipation. This study was designed to compare the safety and efficacy of PEG laxative versus placebo over a 6-month treatment period in patients with chronic constipation. **METHODS:** Study subjects who met defined criteria for chronic constipation were randomized in this double-blind, placebo-controlled, parallel, multicenter study to receive PEG laxative as a single daily dose of 17 g or placebo for 6 months. Baseline constipation status was confirmed during a 14-day observation period. As a primary efficacy variable, treatment success was defined as relief of modified ROME criteria for constipation for 50% or more of their treatment weeks. Various secondary measures were assessed. An Interactive Voice Response System (IVRS) recorded daily bowel movement experience and study efficacy and safety information. Laboratory testing at baseline and monthly for the study duration was analyzed for hematology, blood chemistry including amylase, GGT, uric acid, lipids, and urinalysis. **RESULTS:** A total of 304 patients were enrolled and received treatment at one of 50 centers. Successful treatment according to the primary efficacy variable was seen in 52.0% of PEG and 11% of placebo subjects ($P < 0.001$). Similar efficacy was seen in a subgroup of 75 elderly subjects. According to the primary efficacy definition (based on individual treatment weeks), 61% of PEG treatment weeks versus 22% of the placebo weeks were successful ($P < 0.001$). There were no significant differences in laboratory findings or adverse events except for the gastrointestinal category where diarrhea,

flatulence, and nausea were the most frequent with PEG although they were not individually statistically significant compared with placebo. Similar results were observed when analyzed for differences due to gender, race, or age. **CONCLUSIONS:** PEG laxative is safe and effective for use in patients with chronic constipation for 6 months.

6. Di Stefano, M., E. Miceli, et al. (2007). "Effect of tegaserod on recto-sigmoid tonic and phasic activity in constipation-predominant irritable bowel syndrome." Am J Gastroenterol **102**(8): 1720-6.

OBJECTIVES: In irritable bowel syndrome (IBS), the modulation of neural pathways may be altered and we have recently shown that postprandial recto-sigmoid tone modification is impaired. On pathophysiological grounds, we do not know whether this alteration may have a role in symptom onset and, in particular, whether an effective drug, such as tegaserod, can improve this response together with symptom severity. **METHODS:** Twenty-two female patients with constipation-predominant IBS (IBS-C), diagnosed according to Rome II criteria, were studied. All subjects underwent an evaluation of the presence and severity of IBS symptoms and the recto-sigmoid barostat test to measure fasting and postprandial recto-sigmoid tone and phasic contractility. They were then randomly assigned to receive either tegaserod 6 mg b.i.d (12 patients) or placebo tablets (10 patients) for 4 wk, according to a double-blind protocol. Symptom assessment and recto-sigmoid tone and contractility were re-evaluated at the end of the treatment. **RESULTS:** Both symptom severity and postprandial modification of recto-sigmoid tone improved only in the tegaserod group and a significant correlation was evident between the improvement of bloating and the improvement of postprandial recto-sigmoid tone modification. No effect of tegaserod on recto-sigmoid motility index or correlation between motility index and symptom improvement was evident. **CONCLUSIONS:** In IBS-C female patients, the administration of tegaserod improves symptom severity and is accompanied by an improvement of recto-sigmoid tone response to a meal.

7. Drossman, D. A., W. D. Chey, et al. (2009). "Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies." Aliment Pharmacol Ther **29**(3): 329-41.

BACKGROUND: Effective treatments for irritable bowel syndrome with constipation (IBS-C) are lacking. **AIM:** To assess the efficacy and safety of lubiprostone in IBS-C. **METHODS:** A combined analysis was performed among 1171 patients with a Rome II diagnosis of IBS-C in two phase-3 randomized trials of lubiprostone 8 mcg vs. placebo twice daily for 12 weeks. Using a balanced seven-point Likert scale ranging from significantly relieved (+3), to significantly worse (-3), patients responded on their electronic diary to the question: 'How would you rate your relief of IBS symptoms over the past week compared to how you felt before you entered the study?'. The primary efficacy endpoint was the percentage of overall responders. **RESULTS:** Using an intent-to-treat analysis with last observation carried forward, a significantly higher percentage of lubiprostone-treated patients were considered overall responders compared with those

treated with placebo (17.9% vs. 10.1%, $P=0.001$). Patients treated with lubiprostone reported a similar incidence of adverse events to those treated with placebo.

CONCLUSIONS: The percentage of overall responders based on patient-rated assessments of IBS-C symptoms was significantly improved in patients treated with lubiprostone 8 mcg twice daily compared to those treated with placebo. Lubiprostone was well tolerated with a favourable safety profile.

8. Harish, K., K. Hazeena, et al. (2007). "Effect of tegaserod on colonic transit time in male patients with constipation-predominant irritable bowel syndrome." J Gastroenterol Hepatol **22**(8): 1183-9.

BACKGROUND AND AIMS: Tegaserod is approved for the treatment of constipation-predominant irritable bowel syndrome (C-IBS) in females. The aim of this study was to evaluate the effect of tegaserod on colonic transit time (CTT) and symptoms in male patients with C-IBS. **METHODS:** Forty-four males with C-IBS (Rome II) were enrolled. After a baseline washout period of 2 weeks, 40 patients were randomized to 6 mg twice daily of tegaserod or placebo for 12 weeks. Daily bowel habits and weekly satisfactory relief of symptoms were recorded. Total and segmental CTT were measured using radiopaque markers at baseline and after treatment. **RESULTS:** The mean \pm SD for the total colonic, right colonic, left colonic and rectosigmoid transit time (in hours) were 18.96 \pm 3.92, 7.74 \pm 1.55, 5.64 \pm 1.51 and 5.58 \pm 2.2 in the tegaserod group compared to 22.47 \pm 3.73, 9.69 \pm 2.33, 6.6 \pm 1.32 and 6.18 \pm 2.22 in the placebo group at the end of 12 weeks. There was a statistically significant difference in the total, right and left CTT in the tegaserod group ($P < 0.05$) at the end of treatment. Global satisfactory relief at the end of 12 weeks was 75% in the tegaserod group and 50% in the placebo group ($P > 0.05$). Greater stool frequency occurred in the tegaserod group ($P > 0.05$). There was a significant decrease in the stool consistency at the end of 12 weeks in patients treated with tegaserod ($P < 0.05$). **CONCLUSIONS:** Tegaserod causes significant acceleration of CTT in male patients with C-IBS. Although there was a trend towards improvement in bowel symptoms in the treated group, this effect was not statistically significant.

9. Johanson, J. F., D. A. Drossman, et al. (2008). "Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation." Aliment Pharmacol Ther **27**(8): 685-96.

BACKGROUND: Analyses of a trial in constipated patients indicated that lubiprostone may be an effective treatment for irritable bowel syndrome with constipation. **AIM:** To assess the efficacy and safety of three lubiprostone doses for irritable bowel syndrome with constipation. **METHODS:** 195 irritable bowel syndrome with constipation patients received daily doses of 16 [8 microg twice daily (b.d.)], 32 (16 microg b.d.) or 48 microg (24 microg b.d.) lubiprostone or placebo b.d. for 3 months. Gastrointestinal parameters were recorded in diaries daily by patients. **RESULTS:** After 1 month, lubiprostone showed significantly greater improvements in mean abdominal discomfort/pain scores vs. placebo ($P = 0.023$). After 2 months, all lubiprostone groups showed significantly greater improvements in mean abdominal discomfort/pain scores ($P < 0.039$). After 3

months of treatment, the improvement in each lubiprostone arm was greater than placebo, but the test for trend was no longer significant. Treatment with lubiprostone showed significantly higher rates of gastrointestinal adverse events ($P = 0.020$), especially diarrhoea and nausea. CONCLUSION: Lubiprostone significantly improved gastrointestinal symptoms of irritable bowel syndrome with constipation at all doses. Higher doses of lubiprostone, especially the 48 microg/day group, were associated with more gastrointestinal adverse events. From these data, the 16 microg/day dose demonstrated the optimal combination of efficacy and safety. These results warrant further study of lubiprostone for treatment of irritable bowel syndrome with constipation patients.

10. Johanson, J. F., D. Morton, et al. (2008). "Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation." *Am J Gastroenterol* **103**(1): 170-7.

OBJECTIVES: To assess the efficacy and safety of lubiprostone in adults with chronic constipation. METHODS: This multicenter, parallel-group, double-blind controlled trial enrolled 242 patients with constipation and randomized them to receive oral lubiprostone 24 mcg or placebo twice daily for 4 wk. The primary efficacy end point was the number of spontaneous bowel movements (SBMs; those occurring without use of constipation relieving medications) after 1 wk of double-blind treatment. Other evaluations included SBMs at weeks 2, 3, and 4; bowel movement (BM) characteristics (i.e., consistency and straining); constipation severity; abdominal bloating/discomfort; global treatment effectiveness ratings; and safety assessments. RESULTS: The 120 lubiprostone-treated patients reported a greater mean number of SBMs at week 1 compared with the 122 placebo-treated patients (5.69 vs 3.46, $P = 0.0001$), with a greater frequency of SBMs also reported at weeks 2, 3, and 4 ($P \leq 0.002$). Within 24 h of the first dose of study drug, 56.7% of those given lubiprostone reported a SBM compared with 36.9% of those given placebo ($P = 0.0024$); within 48 h, 80% and 60.7% of these patients reported a SBM ($P = 0.0013$), respectively. Stool consistency, straining, and constipation severity, as well as patient-reported assessments of treatment effectiveness, were significantly improved with lubiprostone compared with placebo at all weeks ($P \leq 0.0003$). The two most common treatment-related adverse events were nausea (31.7%) and headache (11.7%). CONCLUSIONS: In patients with chronic constipation, treatment with lubiprostone produces a BM in the majority of individuals within 24-48 h of initial dosing and improves the frequency as well as other characteristics associated with BMs with short-term (i.e., 4 wk) treatment. The most commonly reported adverse event was mild to moderate nausea, which resulted in treatment discontinuation in 5% of treated patients.

11. Johanson, J. F. and R. Ueno (2007). "Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety." *Aliment Pharmacol Ther* **25**(11): 1351-61.

BACKGROUND: Lubiprostone, a locally acting type-2 chloride channel activator, induces intestinal fluid secretion. AIM: To assess efficacy and safety of oral lubiprostone at

multiple doses for the treatment of chronic constipation. **METHODS:** A total of 129 patients with chronic constipation were randomized to receive lubiprostone (24, 48 or 72 mcg/day) or placebo for 3 weeks. Spontaneous bowel movement (SBM) frequency, rescue medication use, symptom assessments and adverse events (AEs) were tracked. **RESULTS:** Over the double-blinded period, mean SBM frequencies were higher for lubiprostone groups (5.1-6.1) vs. placebo (3.8) and the overall difference was statistically significant ($P = 0.046$). SBM frequencies at week 1 were significantly higher in patients taking lubiprostone 48 or 72 mcg/day ($P < 0.003$) and, at week 2, all three lubiprostone doses yielded significantly higher SBM rates vs. placebo ($P < 0.020$). Significantly larger proportions of patients taking lubiprostone 48 and 72 mcg/day also experienced a SBM on the first treatment day ($P < 0.009$). The most common AEs were nausea, headache and diarrhoea. **CONCLUSIONS:** Lubiprostone improved SBM rates in a dose-dependent manner. AEs were tolerable for most patients. Increased AE severity at 72 mcg/day did not provide a clear risk-to-benefit advantage compared with lubiprostone 48 mcg/day, the dose chosen for subsequent Phase 3 studies.

12. Nurko, S., N. N. Youssef, et al. (2008). "PEG3350 in the treatment of childhood constipation: a multicenter, double-blinded, placebo-controlled trial." *J Pediatr* **153**(2): 254-61, 261 e1.

OBJECTIVE: To establish the efficacy and best starting dose of polyethylene glycol (PEG)3350 in the short-term treatment of children with functional constipation. **STUDY DESIGN:** Prospective, randomized, multicenter, double-blinded, placebo-controlled, dose-ranging study of PEG3350 in children with functional constipation. Patients were randomly assigned to either placebo or 0.2 g/kg per day, 0.4 g/kg per day, or 0.8 g/kg per day of PEG3350 after a 1 week run-in period, followed by 2 weeks of treatment. All received behavior modification. The primary outcome was the proportion of patients with a successful treatment response: ≥ 3 bowel movements (BM) in the second week. **RESULTS:** 103 children (mean, 8.5 +/- 3.1 years) were enrolled. 77%, 74%, and 73% of the 0.2, 0.4, and 0.8 g/kg groups were successfully treated, as compared with 42% receiving placebo ($P < .04$). There was a significant increase in BM ($P < .001$) and straining improvement ($P < .05$) with the different PEG3350 doses. Stool consistency improved significantly for doses 0.4 g/kg or higher ($P < .001$). There was more abdominal pain and fecal incontinence in patients receiving 0.8 g/kg. PEG3350 was well tolerated. **CONCLUSIONS:** This placebo-controlled study confirms the efficacy and safety of PEG3350 for the short-term treatment of children with functional constipation. We recommend a starting dose of 0.4 g/kg per day.

13. On Chan, A. O., W. Mo Hui, et al. (2007). "Efficacy of tegaserod for functional constipation in Chinese subjects: a randomized double-blind controlled trial in a single centre." *Aliment Pharmacol Ther* **25**(4): 463-9.

BACKGROUND: Tegaserod has been shown to be effective in chronic constipation in Western population. Aim We investigated if tegaserod is equally effective in Chinese population. **MATERIALS AND METHODS:** Two hundred and fifty patients were randomized to a

double-blinded 8-week treatment of tegaserod 6 mg b.d. or placebo. Response during weeks 1-4 was defined as an increase in complete spontaneous bowel motion ≥ 1 /week. Secondary efficacy included response during weeks 1-8, individual symptoms and scores, quality of life and global assessment of bowel habits and constipation. RESULTS: One hundred and nine patients from the treatment group and 107 from the placebo group completed the 8-week treatment. Responder rates was 47.7% vs. 29% for the treatment and placebo groups ($P = 0.005$). The sustained complete spontaneous bowel motion rate was 29.4% vs. 15.7% in the two groups ($P = 0.016$). The response rates were higher than that reported previously in the Caucasian studies. There was improvement in the scores for stool form scale, bothersomeness of constipation, abdominal distension/bloating and satisfaction of bowel habit ($P \leq 0.05$). The mental score was higher in the treatment group (46.8 +/- 9 vs. 43.6 +/- 10, $P = 0.01$). CONCLUSIONS: Tegaserod is effective in relieving chronic constipation in Chinese population. The efficacy observed may be higher than that in Western population.

14. Thomson, M. A., H. R. Jenkins, et al. (2007). "Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study." Arch Dis Child **92**(11): 996-1000.

OBJECTIVES: To assess the efficacy and safety of polyethylene glycol 3350 plus electrolytes (PEG+E) for the treatment of chronic constipation in children. DESIGN: Randomised, double blind, placebo controlled crossover trial, with two 2-week treatment periods separated by a 2-week placebo washout. SETTING: Six UK paediatric departments. PARTICIPANTS: 51 children (29 girls, 22 boys) aged 24 months to 11 years with chronic constipation (lasting \geq or =3 months), defined as \leq or =2 complete bowel movements per week and one of the following: pain on defaecation on 25% of days; \geq or =25% of bowel movements with straining; \geq or =25% of bowel movements with hard/lumpy stools. 47 children completed the double blind treatment. MAIN OUTCOME MEASURES: Number of complete defaecations per week (primary efficacy variable), total number of complete and incomplete defaecations per week, pain on defaecation, straining on defaecation, faecal incontinence, stool consistency, global assessment of treatment, adverse events and physical examination. RESULTS: The mean number of complete defaecations per week was significantly higher for children on PEG+E than on placebo (3.12 (SD 2.05) v 1.45 (SD 1.20), respectively; $p \leq 0.001$). Further significant differences in favour of PEG+E were observed for total number of defaecations per week ($p = 0.003$), pain on defaecation ($p = 0.041$), straining on defaecation ($p \leq 0.001$), stool consistency ($p \leq 0.001$) and percentage of hard stools ($p = 0.001$). Treatment related adverse events (all mild or moderate) occurred in similar numbers of children on PEG+E (41%) and placebo during treatment (45%). CONCLUSIONS: PEG+E is significantly more effective than placebo, and appears to be safe and well tolerated in the treatment of chronic constipation in children.

Appendix B. Abstracts of prucalopride RCTs

1. Bouras, E. P., M. Camilleri, et al. (2001). "Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder." *Gastroenterology* 120(2): 354-60.

BACKGROUND & AIMS: Prucalopride (PRU) is a selective benzofuran 5-hydroxytryptamine(4)-receptor agonist with gastrointestinal and colonic prokinetic activities. We evaluated the effects of PRU on gastrointestinal and colonic transit in patients with constipation. **METHODS:** Gastrointestinal and colonic transit were measured over 48 hours in 40 patients who fulfilled modified Rome I criteria for functional constipation. Patients had no evidence of a rectal evacuation disorder. Subjects were randomized to receive a daily dose of 2 or 4 mg PRU or placebo in a double-blind, parallel-group design. Each treatment lasted 7 days. The transit test was performed over the last 48 hours of the study. Effects on gastric emptying, small bowel transit, and colonic transit were analyzed using Kruskal-Wallis and Wilcoxon rank sum tests. **RESULTS:** Of 61 patients screened, 40 were eligible and randomized. Two patients withdrew because of adverse events. PRU accelerated overall gastric emptying and small bowel transit. PRU tended to accelerate overall colonic transit with significantly faster overall colonic transit and ascending colon emptying with the 4-mg dose. **CONCLUSIONS:** PRU accelerates transit through the stomach, small bowel, and colon in patients with constipation unassociated with a rectal evacuation disorder.

2. Camilleri M, Kerstens R, Ryckx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med.* 2008 May 29;358(22):2344-54. **BACKGROUND:** In this 12-week trial, we aimed to determine the efficacy of prucalopride, a selective, high-affinity 5-hydroxytryptamine₄ receptor agonist, in patients with severe chronic constipation. **METHODS:** In our multicenter, randomized, placebo-controlled, parallel-group, phase 3 trial, patients with severe chronic constipation (< or =2 spontaneous, complete bowel movements per week) received placebo or 2 or 4 mg of prucalopride, once daily, for 12 weeks. The primary efficacy end point was the proportion of patients having three or more spontaneous, complete bowel movements per week, averaged over 12 weeks. Secondary efficacy end points were derived from daily diaries and validated questionnaires completed by patients. Adverse events, clinical laboratory values, and cardiovascular effects were monitored. **RESULTS:** Efficacy was analyzed in 620 patients. The proportion of patients with three or more spontaneous, complete bowel movements per week was 30.9% of those receiving 2 mg of prucalopride and 28.4% of those receiving 4 mg of prucalopride, as compared with 12.0% in the placebo group (P<0.001 for both comparisons). Over 12 weeks, 47.3% of patients receiving 2 mg of prucalopride and 46.6% of those receiving 4 mg of prucalopride had an increase in the number of spontaneous, complete bowel movements of one or more per week, on average, as compared with 25.8% in the placebo group (P<0.001 for both comparisons). All other secondary efficacy end points, including patients' satisfaction with their bowel function and treatment and their perception of the severity of their constipation symptoms, were significantly improved with the use of 2 or 4 mg of prucalopride as compared with placebo, at week 12. The most frequent treatment-related adverse events were headache and abdominal pain. There were no significant

cardiovascular effects of treatment. **CONCLUSIONS:** Over 12 weeks, prucalopride significantly improved bowel function and reduced the severity of symptoms in patients with severe chronic constipation. Larger and longer trials are required to further assess the risks and benefits of the use of prucalopride for chronic constipation.

3. Coremans, G., R. Kerstens, et al. (2003). "Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial." *Digestion* 67(1-2): 82-9.

BACKGROUND: Chronic constipation (CC) is common and there is a need for more effective and better-tolerated agents that normalize bowel function without affecting secretion.

Prucalopride is a novel, selective serotonin(4) receptor agonist with enterokinetic properties.

AIMS: Pilot study to compare the efficacy and tolerability of prucalopride and placebo in patients with severe CC referred to a tertiary centre. **METHODS:** After 4-weeks' run in, patients were randomized to 4 weeks' once daily, double-blind treatment with either prucalopride 4 mg (n = 27) or placebo (n = 26). A 50% dose reduction after 2 weeks' treatment was possible for patients with an excessive gastrointestinal response to the study medication (severe cramps, abdominal pain, and diarrhea). Patients assessed efficacy using a visual analogue scale (VAS) and recorded bowel function in daily diaries. The investigator assessed efficacy and total gut transit time (marker study). **RESULTS:** Patient VAS assessment demonstrated that prucalopride was significantly more effective than placebo in softening stools, and decreasing straining and time to first stool. Prucalopride also had a positive effect on stool frequency, feeling of complete evacuation and total gut transit time, although these differences were not statistically significant compared with placebo. The most common adverse events were gastrointestinal symptoms and headache; most were mild to moderate. There were no clinically relevant effects on cardiovascular or laboratory parameters. **CONCLUSIONS:** Once-daily prucalopride 4 mg for 4 weeks is effective and well tolerated in patients with severe CC. It improves whole gut transit, reducing straining, softening stools and reducing time to first bowel movement.

4. Emmanuel, A. V., A. J. Roy, et al. (2002). "Prucalopride, a systemic enterokinetic, for the treatment of constipation." *Aliment Pharmacol Ther* 16(7): 1347-56.

BACKGROUND: Laxatives are frequently ineffective in treating constipation. An alternative therapeutic approach is to target serotonin-4 receptors, which are involved in initiating peristalsis. **AIM:** In a double-blind, placebo-controlled trial, to assess the efficacy and safety of a systemically active serotonin-4 agonist, prucalopride. **METHODS:** Seventy-four women with constipation were stratified into slow or normal transit groups, and each group was randomized to receive either placebo or 1 mg prucalopride daily for 4 weeks. A bowel function diary was maintained. Whole-gut and oro-caecal transit, visceral sensitivity, quality of life and psychological state were assessed before and after treatment. **RESULTS:** Prucalopride, not placebo, increased spontaneous stool frequency (P=0.008) and reduced time to first stool (P < 0.001). Prucalopride reduced the number of retained markers in all patients compared to placebo (P=0.004). Prucalopride reduced the mean number of retained markers in slow transit (P=0.069), but did not alter the marker count in normal transit (P=0.86). Oro-caecal transit was accelerated by prucalopride, not placebo (P=0.004). Prucalopride, not placebo, increased rectal sensitivity to

distension (urge volume, $P=0.01$) and electrical stimulation ($P=0.001$). Prucalopride significantly improved several domains of the Short Form Health Status Survey and the disease-specific quality of life. Adverse effects were similar for prucalopride and placebo. **CONCLUSIONS:** Prucalopride improves symptoms, upper gut transit and gut sensitivity in constipated patients with both slow and normal transit. It improves transit in patients with slow transit. These changes are associated with improved well-being.

5. Quigley, E. M., L. Vandeplasse, et al. (2009). "Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation--a 12-week, randomized, double-blind, placebo-controlled study." *Aliment Pharmacol Ther* **29**(3): 315-28.

BACKGROUND: Chronic constipation may result in disabling symptoms, is often unsatisfactorily treated by laxatives and negatively impacts quality of life (QoL). **AIM:** A randomized, double-blind, placebo-controlled, phase III trial to evaluate the efficacy and safety of a selective, high-affinity 5-HT(4) receptor agonist, prucalopride, in patients with chronic constipation [≤ 2 spontaneous complete bowel movements (SCBMs)/week]. **METHODS:** Placebo, 2 or 4 mg prucalopride was administered orally once daily, for 12 weeks. The primary efficacy endpoint was the proportion of patients with ≥ 3 SCBMs/week, averaged over 12 weeks. Other assessments included BM frequency, constipation-related QoL and symptoms and tolerability. **RESULTS:** Among 641 patients, significantly more patients taking prucalopride 2 or 4 mg (24%) than placebo (12%), achieved the primary efficacy endpoint (≥ 3 SCBMs/week) or an increase of ≥ 1 SCBMs/week; 43% and 47% vs. 28% respectively. Prucalopride-treated patients also achieved significantly greater satisfaction with treatment and bowel function, and improved perception of constipation severity and constipation-related QoL, compared with placebo. Most frequent treatment-related adverse events were headache, abdominal pain, nausea and diarrhoea (mainly during day 1). There were no differences in comparison to placebo in the incidence of serious adverse effects or cardiovascular events. **CONCLUSION:** Over 12 weeks, prucalopride was effective and well tolerated in chronic constipation.

6. Sloots, C. E., A. C. Poen, et al. (2002). "Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation." *Aliment Pharmacol Ther* **16**(4): 759-67.

BACKGROUND: There is a need for better tolerated drugs to normalize bowel function in chronic constipation. Prucalopride is a highly selective, specific, serotonin₄ receptor agonist with enterokinetic properties. **AIM:** To evaluate the effects of prucalopride on bowel function, colonic transit and anorectal function in patients with chronic constipation. **METHODS:** Twenty-eight patients were enrolled in this double-blind, placebo-controlled, crossover study (prucalopride: 1 mg, $n=12$; 2 mg, $n=16$). Patients kept a bowel function diary. Colonic transit times and anorectal function (anal manometry, rectal sensitivity and rectal compliance) were assessed. **RESULTS:** Prucalopride (1 mg) compared to placebo significantly increased the mean number of spontaneous complete, spontaneous and all bowel movements per week. Prucalopride (1 mg) significantly decreased the percentage of bowel movements with hard/lumpy stools and straining and increased the urge to defecate. Prucalopride (1 and 2 mg) decreased the mean total colonic transit time by 12.0 h (prucalopride 42.8 h vs. placebo 54.8 h; $P=0.074$). No statistically

significant effects were found in any of the anorectal function parameters. Prucalopride was well tolerated. There were no clinically relevant changes in standard safety parameters.

CONCLUSIONS: Prucalopride significantly improves stool frequency and consistency, and the urge to defecate, and may decrease colonic transit times in patients with chronic constipation.

7. Tack, J., M. van Outryve, et al. (2009). "Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives." *Gut* **58**(3): 357-65.

OBJECTIVE: To determine the efficacy, impact on quality of life (QOL) and safety of prucalopride, a selective, high-affinity 5-HT(4) receptor agonist, in patients with chronic constipation. METHODS: In this multicentre, randomised, placebo controlled, parallel-group, phase III study, patients with chronic constipation (two or fewer spontaneous complete bowel movements (SCBM)/week) received 2 mg or 4 mg prucalopride or placebo, once daily, for 12 weeks. The primary efficacy endpoint was the proportion of patients reaching three or more SCBM/week. The key secondary efficacy endpoint was the proportion of patients having an increase of one or more SCBM/week. The primary QOL endpoint was the patient assessment of constipation QOL satisfaction subscale score. Safety parameters included adverse events, laboratory values and cardiovascular events. RESULTS: Efficacy was evaluated over 713 patients. Averaged over 12 weeks, higher proportions of patients on prucalopride 2 mg (19.5%; $p < 0.01$), 4 mg (23.6%; $p < 0.001$) had three or more SCBM/week (or normalisation of bowel function) compared with placebo (9.6%). Similar results were seen in the subgroup (83%) of patients dissatisfied with previous laxative treatment. Both doses of prucalopride also significantly improved secondary efficacy and QOL endpoints, including the proportion of patients with an increase of one or more SCBM/week, evacuation completeness, perceived disease severity and treatment effectiveness and QOL. Prucalopride 4 mg significantly reduced the need for straining versus placebo ($p < 0.05$). The most frequent treatment-related adverse events were headache and diarrhoea. Both doses of prucalopride were safe and well tolerated. CONCLUSION: Prucalopride significantly and consistently improved bowel function, associated symptoms and satisfaction in chronically constipated patients.