Systematic review: cardiovascular safety profile of 5-HT4 agonists developed for gastrointestinal disorders

J. Tack*, M. Camilleri†, L. Chang‡, W. D. Chey§, J. J. Galligan†, B. E. Lacy**, S. Müller-Lissner††, E. M. M. Quigley‡‡, J. Schuurkes§§, J. H. De Maeyer§§& V. Stanghellini¶¶

SUMMARY

Background
The nonselective 5-HT4 receptor agonists, cisapride and tegaserod have been associated with cardiovascular adverse events (AEs).

Aim
To perform a systematic review of the safety profile, particularly cardiovascular, of 5-HT4 agonists developed for gastrointestinal disorders, and a nonsystematic summary of their pharmacology and clinical efficacy.

Methods
Articles reporting data on cisapride, clebopride, prucalopride, mosapride, renzapride, tegaserod, TD-5108 (velusetrag) and ATI-7505 (naronapride) were identified through a systematic search of the Cochrane Library, Medline, Embase and Toxfile. Abstracts from UEGW 2006–2008 and DDW 2008–2010 were searched for these drug names, and pharmaceutical companies approached to provide unpublished data.

Results
Retrieved articles on pharmacokinetics, human pharmacodynamics and clinical data with these 5-HT4 agonists, are reviewed and summarised nonsystematically. Articles relating to cardiac safety and tolerability of these agents, including any relevant case reports, are reported systematically. Two nonselective 5-HT4 agonists had reports of cardiovascular AEs: cisapride (QT prolongation) and tegaserod (ischaemia). Interactions with, respectively, the hERG cardiac potassium channel and 5-HT1 receptor subtypes have been suggested to account for these effects. No cardiovascular safety concerns were reported for the newer, selective 5-HT4 agonists prucalopride, velusetrag, naronapride, or for nonselective 5-HT4 agonists with no hERG or 5-HT1 affinity (renzapride, clebopride, mosapride).

Conclusions
5-HT4 agonists for GI disorders differ in chemical structure and selectivity for 5-HT4 receptors. Selectivity for 5-HT4 over non-5-HT4 receptors may influence the agent’s safety and overall risk–benefit profile. Based on available evidence, highly selective 5-HT4 agonists may offer improved safety to treat patients with impaired GI motility.

Aliment Pharmacol Ther 2012; 35: 745–767
**INTRODUCTION**

Disorders of gastrointestinal (GI) motility are considered a major pathophysiological mechanism underlying symptoms of functional GI disorders.1 Therapeutic agents have been designed to stimulate muscle activity to address the underlying hypomotility associated with disorders such as slow-transit constipation, gastroparesis and ineffective oesophageal motility.1 Activation of 5-HT4 receptors on cholinergic nerve endings in the enteric nervous system enhances the release of acetylcholine from motor neurons, thereby stimulating GI propulsive motility.2, 3 Most of the 5-HT4 receptors, thereby stimulating GI propulsive motility.2, 3 From these pharmacological observations, 5-HT4 receptor agonists have been developed for the treatment of hypomotility disorders. Nonselective 5-HT4 receptor agonists such as cisapride and tegaserod were successfully developed for the treatment of hypomotility disorders of the upper and lower GI tract, respectively.4, 5 Although both drugs saw broad clinical use, they were associated with cardiovascular adverse events (AEs).6-8 Cisapride was subsequently withdrawn from the global market in 2000 and, since 2009, tegaserod, which never received approval in the European Union (EU), has been limited to emergency use in the United States.9, 10 These cardiovascular AEs, which may be more related to a lack of selectivity of certain compounds or classes of compounds, rather than to genuine 5-HT4 receptor-mediated effects, have strongly impacted the perceived risk–benefit ratio of 5-HT4 receptor agonists. Meanwhile, a newer generation of selective 5-HT4 receptor agonists is being developed for the treatment of GI motility disorders. In this article, we review the safety profile of older and newer 5-HT4 receptor agonists developed for GI disorders, focusing on their cardiovascular risk profile.

**PHARMACOLOGY OF 5-HT4 RECEPTOR AGONISTS**

**Structure of 5-HT4 receptors**

5-HT4 receptors are heptahelical receptors, which primarily couple to the stimulatory protein Gs and activate the 3′,5′ cyclic adenosine monophosphate-dependent protein kinase A pathway.11, 12 Most of the 5-HT4 receptor splice variants are identical up to leucine 358, but their intracellular C-terminal tails differ.13 The splice variants 5-HT4(a) and 5-HT4(b) have been found in all species studied thus far, with 5-HT4(b) being the dominant splice variant in human tissues.14 Additional splice variants have also been identified in human (h5-HT4(g), h5-HT4(d), h5-HT4(g), h5-HT4(i) and h5-HT4(a)), mouse (m5-HT4(g) and m5-HT4(g)) and rat (r5-HT4(c1) and r5-HT4(c))13, 15, 16 and more recently in porcine tissue.17 The physiological implication of the multitude of splice variants and their differential coupling to signal transduction cascades remains unclear.

Furthermore, several observations suggest that there is cell type-, tissue-specific or disease-state-specific expression (e.g. in gastroparesis) of certain splice variants.13, 18-21 However, currently, there are no drugs which reliably discriminate among 5-HT4 receptor splice variants, but such drugs could provide an interesting alternative opportunity for tissue-specific drug targeting.

**Tissue distribution of 5-HT4 receptors**

5-HT4 receptors are localised to neurons in the central nervous system, including the prefrontal cortex,12, 22 hippocampus12, 22 and mesolimbic and nigrostriatal dopamine systems.24 Functional 5-HT4 receptors are also found in the GI tract, bladder and heart.3, 25, 26

In the GI tract, 5-HT4 receptors are expressed in enteric neurons27 as well as smooth muscle cells.28-30 As a major consequence of 5-HT4 receptor activation, acetylcholine is released from interneurons and motor neurons, thus increasing propulsive motility.30-37

**Classes of 5-HT4 receptor agonists**

Several different classes of 5-HT4 receptor agonists have been developed for the treatment of GI disorders. We review those classes here, focusing on their affinity and selectivity for the 5-HT4 receptor, as well as any tissue-dependent agonism (partial or full agonism) that might arise (in part) from differences in receptor reserve or coupling efficiency between different tissues.38 Whether or not a drug is a full or partial agonist in a given tissue may depend on the receptor concentration or the efficiency of the receptor-effector coupling. Thus, it may be feasible to obtain a certain degree of tissue selectivity with a low efficacy agonist or low doses of a high efficacy agonist (in favour of tissues with high receptor reserve for the given agonist, such as the GI tract), as tissues with no receptor reserve for the agonist would not be stimulated by this drug.

**Benzamides.** The substituted benzamides, including metoclopramide, cisapride, renzapride, mosapride, clebopride and naronapride (ATI-7505) are 5-HT4 receptor agonists with moderate affinity and poor selectivity for the 5-HT4 receptor (Figure 1).2 Metoclopramide is also an antagonist at D2 dopamine receptors and at 5-HT3 receptors, while cisapride blocks 5-HT2 and 5-HT3 receptors and the human ether-a-go-go-related gene (hERG)-encoded K+ channel.39, 40 The consequences of
these interactions are clearer for some than for others; for example, the prolongation of cardiac action potential repolarisation and, thus, QT (the time elapsing from the beginning of the QRS complex to the end of the T wave in an electrocardiogram) interval, due to the blockade of the hERG channel by cisapride, is likely to underlie the arrhythmogenic potential of this nonselective 5-HT₄ receptor agonist. These non-5-HT₄ receptor sites of action, coupled with their tissue-dependent pharmacodynamics, complicate the description of the actions of benzamides in vivo.

In the rat oesophagus, 5-HT₄ receptors are localised to the muscularis mucosae (smooth muscle), where they mediate relaxation. In this tissue, cisapride, renzapride and mosapride have 80–90% of the intrinsic activity of 5-HT. In the guinea-pig distal colon, cisapride, renzapride and mosapride mediate a contractile response and have 80–100% of the intrinsic activity of 5-HT. Therefore, in both the guinea pig colon and rat oesophagus, benzamides are full agonists. In contrast, in the guinea pig ileum, cisapride, renzapride and mosapride have only 50–60% of the intrinsic activity of 5-HT. Similarly, cisapride has <60% of the intrinsic activity of 5-HT in relaxing circular muscle strips of the canine rectum.

Little preclinical information is available on naronapride, another substituted benzamide 5-HT₄ receptor agonist designed to have the same therapeutic benefit as cisapride, but without the side effects. Naronapride is structurally similar, but more selective, than cisapride, with minimal hERG channel activity as well as minimal-

---

**Figure 1 | Molecular structure of 5-HT₄ agonists.**
to-no activity at 5-HT<sub>3</sub> receptors. Naronapride stimulates GI motility in vivo in dogs and in humans.

**Carbazimidamides.** Tegaserod is an indole carbazimida-mide agonist with high affinity for the 5-HT<sub>4</sub> receptor, but it is also a 5-HT<sub>2a</sub> and 5-HT<sub>2b</sub> receptor antagonist and 5-HT<sub>1</sub> receptor agonist (Figure 1). The contribution of 5-HT<sub>2b</sub> receptor antagonism to the therapeutic actions of tegaserod on gut motility remains unknown. Early studies showed that tegaserod facilitates the peristaltic reflex in vitro in human small intestine, and guinea pig and rat colonic preparations.

When agonist-evoked contractions of the guinea pig ileum were studied, tegaserod was equipotent with 5-HT, but had only 30% of the intrinsic activity of 5-HT. In vitro studies comparing 5-HT<sub>4</sub> receptor-mediated relaxation of canine rectal smooth muscle showed that tegaserod was 10-fold less potent than 5-HT and had only 55% of the intrinsic activity of 5-HT. In the porcine stomach, tegaserod had approximately the same intrinsic activity as 5-HT when increases in cholinergic neurogenic contractions were measured. These data indicate that tegaserod is a potent 5-HT<sub>4</sub> receptor agonist in all tissues tested. While tegaserod is frequently identified as a partial receptor agonist, this property is tissue-dependent.

**Benzofurancarboxamides.** Prucalopride belongs to the class of benzofurancarboxamide agonists, which have high affinity and selectivity for the 5-HT<sub>4</sub> receptor, and tissue-specific agonist activity (Figure 1). The most pronounced effect of prucalopride is stimulation of colonic motility.

5-HT<sub>4</sub>-HT<sub>4</sub> receptors are a widely expressed and dynamic class of receptors and 5-HT<sub>4</sub> receptor agonists are effective stimulants of GI motility. Differences in the pharmacology of 5-HT<sub>4</sub> receptor agonists originates mainly from differences in their selectivity for 5-HT<sub>4</sub> over other receptor types, such as 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptors, and the hERG channel (Table 1), or by their degree of tissue-specific agonism.

**METHODS**

The purpose of this review was to comprehensively search and systematically review the evidence on the safety of 5-HT<sub>4</sub> receptor agonists developed for GI disor-
Systematic review: cardiovascular safety profile of 5-HT₄ agonists

ders, with particular reference to cardiovascular safety. Literature on pharmacokinetics, human pharmacodynamics and clinical data was also collected systematically, but summarised non-systematically and therefore not presented here in full.

An independent researcher at the Royal Society of Medicine Library Search Services performed a comprehensive search of the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database and the NHS Economic Evaluation Database), Medline (1949 – April 2009), Embase (1974 – April 2009) and ToxFile (1900 – April 2009) in June 2009. The search encompassed all types of clinical trials as well as systematic reviews, meta-analyses and case reports, using the terms ‘cisapride’ OR ‘clebopride’ OR ‘prucalopride’ OR ‘mosapride’ OR ‘renzapride’ OR ‘tegaserod’ OR ‘TD-5108’ OR ‘ATI-7505’, including derivatives of these terms and other names used for these drugs. Limits applied were: English language, humans and adults. No date limitation was imposed. The searches were repeated in June 2010 to identify any new reports that emerged during the time taken to develop the manuscript. Upon revision of the manuscript in December 2011, an additional search for pharmacokinetic information was conducted and relevant references were obtained. Authors also contacted the medical information departments of relevant pharmaceutical companies to request further unpublished information or abstracts presented at conferences. The reference lists of retrieved articles were also reviewed.

Abstracts presented at UEGW 2006–2008 and at DDW 2008–2010 (i.e. for all years where abstracts were searchable electronically) were also searched by medical writing support staff, for mention of the drugs of interest (listed above), and those reporting data not already published in the retrieved articles were included in the analysis.

The Royal Society of Medicine use an automated duplicate checker, followed by hand-screening by the researcher to remove duplicates before records were reviewed. The remaining abstracts were filtered for relevance according to predefined eligibility criteria: studies had to relate to GI disorders, to the study drug (listed above), be either clinical studies or systematic reviews (including meta-analyses) and case reports were only included if they related to cardiac safety. Resulting abstracts were then hand-searched against the same eligibility criteria by a second reviewer, and relevant abstracts were segregated into pharmacokinetics, human pharmacodynamics, clinical studies and safety/tolerability, and full-text of these articles obtained. Full text was then reviewed independently by the authors. Cardiac-related safety/tolerability information was systematically reviewed and data retrieved from the full text by the authors were included in the manuscript, as the study authors had originally reported (without using any specific summary measures or additional analyses). Any discrepancies were discussed with the authors. No specific form was used to extract data, risk of bias of individual studies was not formally assessed and data from individual studies were not combined.

RESULTS

The literature searches, after removal of duplicates, returned a total of 1164 articles. A total of 61 conference abstracts were identified.

The original cisapride search returned 582 articles. Of these, 381 were selected for full-text review (20 pharmacokinetic, 141 pharmacodynamic, 183 clinical efficacy, 37 safety). Of these, 75 were considered relevant and cited in this article; 31 additional articles were identified and included. In the 2010 update to the search, four articles were identified, two of which met inclusion criteria. None of the three conference abstracts identified were considered relevant.

The tegaserod search returned 162 articles in the original search, and 13 in the update. Of these, 100 were selected for full-text review and 22 were considered relevant and cited in this article; nine additional articles were identified and included. Upon revision of the manuscript in 2011, one additional article was identified in the search and included in the manuscript. None of the 19 conference abstracts identified was included in this report.

The renzapride search returned 105 articles in the original search and two in the update. Of these, 17 were selected for full-text review and seven were considered relevant and cited in this article; two additional articles were identified and included. Upon revision of the manuscript in 2011, one additional article was identified in the search and included in the manuscript. No renzapride conference abstracts were identified.

The clebopride search returned 58 results, of which 38 were selected for full-text review. Of these, eight were included in this report (two of these were originally excluded for not meeting inclusion criteria, but provided useful supporting information so were included by the author). Of the 16 safety-related articles selected for full-text review, none related to cardiac safety; two represen-
Nonselective 5-HT₄ receptor agonists

Historically, metoclopramide was the first 5-HT₄ receptor agonist to be used for the treatment of hypomotility disorders. The drug is also a D₂ receptor antagonist, an action which underlies the well-established, potentially irreversible, neurological side effects that may occur with metoclopramide intake, and therefore will not be described in detail.

Cisapride. Cisapride, an agonist at 5-HT₄ receptors and an antagonist at 5-HT₃ and 5-HT₂ receptors, was introduced worldwide in the 1990s, and has widespread prokinetic effects throughout the GI tract. Although originally employed in a wide range of motility disorders, cisapride was approved for the treatment of acute and severe exacerbations of demonstrated chronic idiopathic or diabetic gastroparesis after failure of other treatment options in the EU, and was approved by the U.S. Food and Drug Administration (FDA) for nocturnal heartburn only.

Pharmacokinetics and pharmacodynamics. The pharmacokinetics and pharmacodynamics of cisapride are summarised in Tables 2 and 3 respectively.

Clinical trials. Clinical trials, summarised in Supplementary Table S1, have explored the efficacy of cisapride in a number of GI conditions, including GERD, functional dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, post-operative ileus and chronic constipation, but evidence of an effect was not robust enough to obtain regulatory approval for indications other than nocturnal heartburn. In 2000, cisapride was withdrawn from the market worldwide, due to concerns over cardiovascular safety (see safety and tolerability section).

Safety and tolerability. Initial experience with cisapride, including post-marketing data from two study populations totalling over 23,000 patients, suggested that the drug was remarkably safe, with diarrhoea (incidence 4.1%), abdominal pain (1.6%), nausea or vomiting (1.5%), headache (1.4%) and constipation (1.2%) being the most frequently reported AEs. In an epidemiological study of almost 37,000 patients prescribed cisapride in the UK and Canada, serious cardiac rhythm disorders were not found to be inordinately associated with cisapride use; however, the 95% confidence interval was large (0.2–9.8), such that an increase in risk could not be ruled out definitively. In children without underlying cardiac disease or electrolyte imbalance, cisapride was found to have no significant effect on cardiac electrical function, and a meta-analysis of randomised, controlled clinical trials among children with GERD found that although there was no evidence of adverse or harmful events, there were no significant clinical benefits.

Reports of cardiac events began to accumulate, including palpitations and instances of an unusual tachycardia, torsades de pointes, as well as ventricular fibrillation and sudden death started to appear. It soon
Table 2 | Pharmacokinetics of 5-HT₄ agonists

| S-HT₄ receptor agonist | Bioavailability | Plasma levels ($t_{max}$) | Protein binding | $T_{1/2}$ | Metabolism and elimination (hepatic) | Metabolism and elimination (renal) |
|------------------------|----------------|---------------------------|-----------------|---------|------------------------------------|----------------------------------|
| **Nonselective 5-HT₄ receptor agonists** |            |                           |                 |         |                                    |                                  |
| Cisapride              | ~40–50% (absolute) | 1–2 h<sup>141</sup> | ~98%<sup>141</sup> | ~10 h<sup>140</sup> (potentially prolonged in patients with hepatic impairment/elderly)<sup>142</sup> | P450 enzyme system<sup>140</sup> | Unchanged renal or faecal recovery are <10% of the ingested dose following oral administration |
| Tegaserod              | 11 ± 3% (absolute)<sup>143</sup> | 1.3 h<sup>143</sup> | ~98%<sup>144</sup> | 11 ± 5 h (terminal)<sup>143</sup> | In vitro studies suggest that CYP-mediated metabolism plays an insignificant role in the elimination of tegaserod<sup>145</sup> | Transported by P-glycoprotein efflux pump<sup>146</sup> 2/3 excreted unchanged in faeces; 1/3 excreted in urine as main metabolite<sup>144</sup> after acid-catalysed hydrolysis in the stomach and glucuronidation |
| Renzapride             | Good<sup>94</sup> | ~1.4 h<sup>94</sup> | ~6 h (plasma)<sup>94</sup> | Not metabolised through major CYP drug-metabolising enzymes and does not inhibit CYP450-mediated metabolism of other drugs<sup>147</sup> | Renal excretion<sup>95</sup>; eliminated unchanged in the urine<sup>94</sup> |
| Clebopride             | Good<sup>148</sup> | 1.5–1.6 h<sup>149</sup> | 36.5 (0.5 mg) and 26.5 (1 mg) h (serum)<sup>149</sup> | CYP3A4 metabolisation<sup>150</sup> | Excreted in faeces (maximal excretion 2–3 h after ingestion)<sup>148</sup> About 50% renal excretion<sup>151</sup> |
| Mosapride              | 8% (in dogs) and 14% (in monkeys; oral)<sup>152</sup> | 0.5–1.0 h<sup>153</sup> | Hepatic metabolism<sup>120</sup>; first-pass in the liver (principal metabolite M1), excreted in both urine and faeces<sup>153, 154</sup> | Elimination via urine and faeces<sup>155</sup> |
| **Selective 5-HT₄ receptor agonists** |            |                           |                 |         |                                    |                                  |
| Prucalopride           | >90% (oral)<sup>156</sup> | 2.1 ± 0.9 h | 28–33% | 21.2 ± 3.7 h (terminal) | No hepatic metabolism | At least 6% excreted unchanged in faeces<sup>156</sup> | ~60% excreted unchanged in urine<sup>156</sup> |
| Velusetrag             | ~30% (estimate; oral) | 4–6 h | ~13 h | Hepatic metabolism, substrate of CYP3A4 and P-glycoprotein<sup>55</sup> | Major metabolite (THRX-830449) has equivalent potency to parent; elimination $t_{1/2}$ 16 h (single dose) & 35 h (multiple dose)<sup>133</sup> |
| Naronapride            |            |                           |                 |         | No CYP450 metabolisation<sup>44</sup> | Excretion in faeces (one third, unchanged) and urine (metabolite)<sup>157</sup> |
| Pharmacodynamics of 5-HT4 agonists | Cisapride | Tegaserod | Renzapride | Clebopride | Mosapride | Prucalopride | Velusetrag | Naronapride |
|-----------------------------------|-----------|-----------|------------|------------|-----------|--------------|------------|-------------|
| Oesophagus                         |           |           |            |            |           |               |            |             |
| Salivary flow                      | ↑ in GERD 158-168 |           |            |            |           |               |            |             |
| Oesophageal peristalsis/amplitude | ↑ in GERD 158-168 |           |            |            |           |               |            |             |
| Oesophageal emptying               | ↑ in GERD 158-168 |           |            |            |           |               |            |             |
| Oesophageal acid clearance         | ↑ in GERD 158-168 |           |            |            |           |               |            |             |
| Oesophageal acid exposure time     |           | Reduced in GERD 175 |            |            |           |               |            |             |
| No. of reflux events, and no. >5min | ↑ in HV 161, 169, 170, 176 |           |            |            |           |               |            |             |
| LES pressure                       | ↑ or ↓ in GERD 160-162, 168, 177 |           |            |            |           |               |            |             |
| LES tone                           | ↑ 173, 179 |           |            |            |           |               |            |             |
| No. of TLESRs                      | +/− in HV 177, 180 |           |            |            |           |               |            |             |
| Stomach & duodenum                 |           |           |            |            |           |               |            |             |
| Post-prandial acid secretion/gastric acidity | +/− in GERD 165, 177, 181, 182 |           |            |            |           |               |            |             |
| Electrogastrographic patterns      | Improved in FD 183, 184 |           |            |            |           |               |            |             |
| Gastric tone                       | ↑ in GP 185 |           |            |            |           |               |            |             |
| Gastric emptying time              | ↓ in HV 186-189 and patients 164, 185, 188, 190-199 but inconsistent 200-202 |           |            |            |           |               |            |             |
| Gastric compliance/gastric accommodation | +/− in HV 208, 209 |           |            |            |           |               |            |             |
| Gastric transit time               | ↑ in FD and HV 210 |           |            |            |           |               |            |             |
| Gastro-duodenal transit time       |           |           |            |            |           |               |            |             |
| Relaxation of pyloric sphincter    |           |           |            |            |           |               |            |             |
Table 3 | (Continued)

|                      | Cisapride | Tegaserod | Renzapride | Clebopride | Mosapride | Prucalopride | Velusetrag | Naronapride |
|----------------------|-----------|-----------|------------|-------------|------------|--------------|------------|-------------|
| **Antroduodenal motility** | ↑ in HV188, 209, 213, and patients197, 200, 214-216, but inconsistent182, 185, 188 | | | | | | | |
| **Duodenal and jejunal contractions** | | | | | | | | |
| Gall bladder emptying | ↑ in HV217, 218 | | | | | | | |
| **Stomach & intestines** | | | | | | | | |
| Gastrointestinal transit time | | | | | | | ↓ in IBS-C99 | |
| **Small & large intestine** | | | | | | | | |
| Small intestine motility | ↑ in HV219-222 and IBS220, 223 | | | | | | | |
| Small intestine transit time | – in HV,187 | | | | | | | |
| Gall bladder emptying | ↑ in HV217, 218 | | | | | | | |
| Ascending colon emptying | ↓ in HV219-222 and IBS220, 223 | | | | | | | |
| Colonic filling | ↑ in HV219-222 and IBS220, 223 | | | | | | | |
| Colonic transit time | ↓ in HV225 and constipation126-229 | ↓ in HV and IBS-C171, 172 | ↓ in IBS-C96, 99 | ↓ in HV243 and C211 | ↓ in HV207 | ↓ in HV207 | ↓ in HV44 | |
| Colonic motor activity | ↑ after resection230 | | | | | | | |
| Anorectal function | – in HV51, 231 and C232 | | | | | | | |
| Anorectal sensation | ↑ in HV233 | | | | | | | |
| Stools | | | | | | | | |
| Stool consistency | | | | | | ↓ in HV207 | ↓ in HV44 | |
| Bowel frequency | | | | | | ↑ in HV207 | | |
| Whole gut transit | | | | | | ↓ in HV207 | ↓ in HV44 | |

↑, increased; ↓, decreased; –, no effect; +/-, mixed effects; AN, anorexia nervosa; C, constipation; CI, critical illness; CIIP, chronic idiopathic intestinal pseudo-obstruction; DPAN, diabetic patients with autonomic neuropathy; DGp, diabetic gastroparesis; FD, functional dyspepsia; Gp, gastroparesis; HV, healthy volunteers; IBS-C, constipation-predominant irritable bowel syndrome; LES, lower oesophageal sphincter; PD, Parkinson’s disease; TLESR, transient lower oesophageal sphincter relaxations.
came to be recognised that cisapride use could result in prolongation of the QT interval and, thereby, increase the risk of arrhythmia, a phenomenon well described in association with a number of other drugs, most notably quinidine, but including procarbazine, sotalol, amiodarone, disopyramide, macrolide antibiotics (including erythromycin), astemizole, terfenadine, phenothiazines and tricyclic antidepressants. An increased risk was present when cisapride levels were higher, e.g. through concomitant use of CYP450 inhibitors. Indeed, the majority of cardiac AEs occurred when cisapride was used in patients with other risk factors, which included co-administration with other drugs (e.g. triazole antifungals and retrovirals) and foods such as grapefruit juice, which inhibit hepatic cytochrome (CYP) P450 3A4 resulting in high plasma levels of cisapride, or that also caused QT prolongation, as listed above. It also became clear that the likelihood of arrhythmia in association with cisapride use was greater among those with serious underlying disease states such as heart disease, heart failure, respiratory failure, renal failure, hypokalaemia or hypomagnesaemia.

Subsequently, the cellular and molecular basis for the arrhythmogenic potential of cisapride was revealed. In vitro studies found cisapride to be a potent and dose-dependent blocker of the hERG channel, which is the main channel responsible for the repolarisation phase of the cardiac action potential, such that hERG blockade (or channel mutations) prolong the duration of the action potential by delaying the repolarisation phase.

Other studies suggested that it was not QT prolongation per se, but rather, the increase in dispersion of repolarisation that usually accompanies QT prolongation, which provides the arrhythmogenic substrate. Although some studies suggested that cisapride had a low arrhythmogenic potential among neonates regardless of gestational age, others drew attention to the low levels of CYP 3A4 in the neonatal liver and the consequent effects on cisapride metabolism. Indeed, a pharmacokinetic study in premature infants demonstrated increased serum concentrations of cisapride and parallel prolongations of the QT interval.

Unfortunately, around the same time, the prokinetic properties of erythromycin had begun to be widely appreciated and its co-administration with cisapride, or the sequential use of i.v. erythromycin and oral cisapride, was not uncommon; thus, increasing the potential for QT prolongation, through its own effects on the QT interval as well as through its inhibition of CYP450. Others at risk were those with congenital prolongation of the QT interval, a family history of the long QT syndrome or those with significant bradycardia.

As large surveys in adults, children and neonates had indicated that such events were rare and that risks could be managed by an appropriate awareness programme, the initial response was a risk management programme identifying those at risk, as well as drugs that should not be co-administered with cisapride. Accordingly, in 1995, a ‘black box’ warning contraindicating the use of cisapride among those taking drugs that affected its metabolism was issued by the FDA. At that time, 34 cases of torsades de pointes, 23 of prolonged QT interval and 4 deaths had been reported. In 1996, further warnings were issued in relation to concomitant medications that also prolonged the QT interval and in conditions that predisposed to cardiac arrhythmias. As a result, the ‘black box’ was expanded in 1998. However, the subsequent realisation that serious cardiac AEs could occur among low-risk groups, including children, coupled with the documentation of continued cisapride use in contraindicated situations led to the commercial, worldwide withdrawal of the drug in July 2000.

Tegaserod. Tegaserod is a 5-HT4 receptor agonist with a high affinity for 5-HT4 receptors, but also relevant affinity for 5-HT2(a/b), and 5-HT1a(b/d) receptors. Tegaserod was approved in many countries for the treatment of IBS-C and chronic idiopathic constipation. In March 2007, tegaserod was withdrawn from most markets owing to an increased risk of cardiovascular AEs. It was reintroduced in the USA in July 2007 under a treatment investigational new drug protocol for IBS-C and chronic idiopathic constipation in women younger than 55 who are not at risk for certain cardiovascular events. Tegaserod was not approved for use in the EU as the Committee for Medicinal Products for Human Use was of the opinion that the benefit of tegaserod treatment did not outweigh its risks.

Pharmacokinetics and pharmacodynamics. The pharmacokinetics and pharmacodynamics of tegaserod are summarised in Tables 2 and 3 respectively.

Clinical studies. While the benefit of tegaserod therapy in patients with IBS-C has been fairly well demonstrated, evidence of efficacy in chronic idiopathic constipation and functional dyspepsia has been less convincing (summarised in Supplementary Table S2).

Safety and tolerability. The frequency of reported AEs in the 3-month trials with tegaserod varies considerably
change over a 12-month period with open treatment. This was not dose-related. Diarrhoea occurred mainly in patients taking tegaserod (0.44%) and those on placebo (0.41%).

Regarding abdominal surgery in patients with IBS-C, a meta-analysis of 13 controlled trials was conducted, which found no significant difference in the rates of abdominal and pelvic surgery between patients receiving tegaserod (0.44%) and those on placebo (0.41%).

Three AEs potentially attributable to tegaserod have gained particular attention, namely an increased rate of abdominal surgery, ischaemic colitis and cardiac events. They occurred so infrequently that they are unlikely to be identified in Phase III trials and may only come up in pooled analyses or during post-marketing surveillance, but they are severe enough to warrant concerns. Only diarrhoea was reproducibly more prevalent in the tegaserod than in the placebo groups, but this was not dose-related. Diarrhoea occurred mainly in the first week of treatment and was often transient, resolving with continued treatment. The safety profile did not change over a 12-month period with open treatment: headache became the most prevalent AE (10–15%); all other AEs, in particular diarrhoea, ranged below 10%.

Patients with IBS have a higher risk of developing colonic ischaemia than the general population. No cases of ischaemic colitis occurred in over 11 600 patients participating in clinical trials with tegaserod. Although post-marketing reports have noted cases of ischaemic colitis and intestinal ischaemia in patients taking tegaserod, the incidence appears to be similar to the general population and is less than estimates for the IBS patient population. Moreover, no mechanism has been identified through which tegaserod might predispose to ischaemic colitis.

The pre-marketing data of systematic cardiac safety assessment may be summarised as follows: in three randomised, double-blind, controlled, parallel-group clinical studies with more than 2500 IBS patients, prolongation of the QTc interval was similarly frequent between groups, as was the frequency of overall electrocardiographic abnormalities. No ventricular or supraventricular tachycardia was observed. In healthy volunteers, tegaserod at i.v. doses resulting in plasma concentrations up to 100 times those measured after therapeutic doses (6 mg b.d.) did not influence electrocardiographic variables. Data collected from over 18 000 patients demonstrated cardiovascular AEs (myocardial infarction, unstable angina pectoris, stroke and one sudden death) in 13 of 11 614 patients treated with tegaserod (a rate of 0.11%) compared with 1 of 7031 patients treated with placebo (a rate of 0.01%). Therefore, in 2007, the FDA requested withdrawal from the market, citing a relationship between prescriptions of the drug and increased risks of heart attack or stroke. However, this was denied by the manufacturer, as all affected patients were said to have pre-existing cardiovascular disease or risk factors for such. Thus, no causal relationship between tegaserod use and cardiovascular events had been demonstrated. Indeed, a matched case–control study of tegaserod-treated patients with untreated patients found no association between tegaserod and adverse cardiovascular outcomes.

A hypothetical mechanism for tegaserod-related cardiac events was proposed involving interaction at 5-HT₄(b/d) receptors on coronary arterioles. However, as tegaserod does not behave as a 5-HT₁(b) receptor agonist in a recent study of human isolated proximal and distal coronary arterioles, the mechanisms involved remain unclear.

Renzapride. Renzapride, a 5-HT₄ receptor agonist and a 5-HT₃ receptor antagonist, has been evaluated in the treatment of IBS-C, but has not been approved in any part of the world.

Pharmacokinetics and pharmacodynamics. The pharmacokinetics and pharmacodynamics of renzapride are summarised in Tables 2 and 3 respectively.

Clinical studies. Clinical studies with renzapride have focused mainly on IBS (summarised in Supplementary Table S3). However, therapeutic margins were only minimal (5–6% over placebo), and this led to the discontinuation of the drug development programme.

Safety and tolerability. Renzapride was well tolerated; most AEs were mild-to-moderate in intensity and equally distributed across active or placebo treatment groups. The most common AEs were GI, with diarrhoea and abdominal pain being the most commonly associated with renzapride treatment.

In vitro cardiac conductivity studies in isolated Purkinje fibres showed no significant QT prolongation by renzapride. In transfected cells, renzapride was a 1000-fold less potent inhibitor of the hERG channel compared...
with cisapride.\textsuperscript{100} In the clinical trial programme, no significant ECG alterations were observed (in particular no evidence of prolongation of the QT interval).\textsuperscript{95–99, 101}

**Clebopride.** Clebopride is a D\textsubscript{2} receptor antagonist, as well as a 5-HT\textsubscript{4} receptor agonist and a 5-HT\textsubscript{3} receptor antagonist.\textsuperscript{102} Clebopride is available in Italy and Spain as a gastroprokinetic drug.

**Pharmacokinetics and pharmacodynamics.** The pharmacokinetics and pharmacodynamics of clebopride are summarised in Tables 2 and 3 respectively.

**Clinical studies.** To our knowledge, the effects of clebopride on lower GI motility and therapeutic potential in lower GI indications have not been explored. Controlled studies investigating the effects of clebopride have primarily focused on FD, but are dated and are generally underpowered with methodological flaws compared with current requirements of good clinical practice (summarised in Supplementary Table S4).

**Safety and tolerability.** Antagonism of dopamine receptors in the GI tract promotes coordinated motor activity and accelerates transit, while blockade of D\textsubscript{2} receptors in the area postrema exerts an anti-nausea, anti-emetic effect.\textsuperscript{103, 104} However, central D\textsubscript{2} receptor blockade is also responsible for AEs, including extrapyramidal dystonic reactions and hyperprolactinaemia.\textsuperscript{105} Comparative studies among prokinetics have demonstrated that clebopride is most associated with dystonic reactions\textsuperscript{106, 107} that are not limited to reversible Parkinsonian-like symptoms, but also include tardive, potentially irreversible, dyskinesia.\textsuperscript{108} The calculated prevalence of movement disorders associated with chronic use of other antiparkinsonergics is around 1%,\textsuperscript{109} but it is 4-fold higher for clebopride.\textsuperscript{110} Conversely, clebopride exerts a less pronounced hyperprolactinaemic effect compared with any other antiparkinsonergic drug.\textsuperscript{105}

Substituted benzamides have been associated with dose-dependent cardiac AEs. Thus, although overt cardiotoxicity has not been reported in clinical studies on clebopride, the effects of the drug on cardiac action potential duration, hERG channel, and sodium channel currents were investigated in vitro.\textsuperscript{111} Clebopride (10 \textmu M) prolonged the action potential duration at 90% (but not 50%) repolarisation. Furthermore, an IC\textsubscript{50} value of 0.62 ± 0.30 \textmu M for hERG channel currents was determined. No effect was observed on sodium channel currents.\textsuperscript{111} It was concluded that clebopride is sufficiently safe at therapeutic doses, but overdosing or impaired metabolism might be associated with torsadogenic effects.

**Mosapride.** Mosapride is primarily a selective 5-HT\textsubscript{4} receptor agonist in the GI tract.\textsuperscript{112–114} Its principal metabolite is approximately 50% as potent as the parent compound at stimulating gastric motility, however, it is also a potent 5-HT\textsubscript{3} receptor antagonist.\textsuperscript{115} Mosapride is available as a prokinetic agent in a number of Asian countries.

**Pharmacokinetics and pharmacodynamics.** The pharmacokinetics and pharmacodynamics of mosapride are summarised in Tables 2 and 3 respectively.

**Clinical trials.** Several studies have been performed to assess the efficacy of mosapride for the treatment of FD. However, most studies were small and lack controls and, as such, failed to show significant symptomatic improvements (summarised in Supplementary Table S5).\textsuperscript{116}

**Safety and tolerability.** In contrast to cisapride, mosapride does not appear to have any significant effect on K\textsuperscript{+} channels. Using isolated rabbit Purkinje fibres and ventricular muscle, mosapride had little effect on the rapid component of the delayed rectifying K\textsuperscript{+} channels and no effect in hERG transfected cells.\textsuperscript{39, 117, 118} Using a rabbit model of the acquired long-QT syndrome, cisapride prolonged the QT interval, while mosapride did not,\textsuperscript{117} despite its metabolism by CYP3A4.\textsuperscript{119} In a 14-day study of mosapride (15 mg/day) in 10 healthy male volunteers, no ECG changes were noted despite co-administration of erythromycin.\textsuperscript{120} In a separate study of 20 healthy volunteers who received a single dose of mosapride (10 mg), pulse, heart rate, QT interval and ECGs were no different after drug administration.\textsuperscript{121} Furthermore, in a study of 18 patients who were taking a variety of psychiatric medications, co-administration of mosapride did not change any ECG parameters.\textsuperscript{122} However, a case report described a 68-year-old man with sick sinus syndrome, requiring a permanent pacemaker and concomitant flecainide therapy, who developed a prolonged QTc interval after starting mosapride.\textsuperscript{123} In summary, the studies published to date demonstrate that mosapride is safe without any significant cardiovascular effects.

**Selective 5-HT\textsubscript{4} receptor agonists**

**Prucalopride.** Prucalopride is a dihydrobenzofurancarb oxamide derivative with distinct structural differences
from other 5-HT₄ receptor agonists such as cisapride and tegaserod. These differences are likely to account for the greater selectivity for the 5-HT₄ receptor observed with prucalopride (>150× for prucalopride vs. <1 for cisapride and tegaserod). Prucalopride was recently approved, on 15 October 2009, by the European Medicines Agency (EMA) for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

**Pharmacokinetics and pharmacodynamics.** The pharmacokinetics and pharmacodynamics of prucalopride are summarised in Tables 2 and 3 respectively.

**Clinical trials.** The majority of clinical studies with prucalopride were conducted in patients with chronic constipation (summarised in Supplementary Table S6). Multiple randomised, controlled trials found that prucalopride at doses of 1–4 mg (q.d.) improved symptoms of chronic constipation, including stool frequency, stool consistency, straining and quality of life. To date, no studies addressing the efficacy of prucalopride in the IBS-C or upper GI disorders, such as gastroparesis or FD, have been presented.

**Safety and tolerability.** Safety assessments were performed as part of the Phase III studies. Treatment-associated AEs were reported in 70–80% of patients randomised to placebo, 2 or 4 mg of prucalopride. The most common treatment-associated AEs included headache in 25–30% of prucalopride subjects vs. 12–17% of placebo; nausea (12–24% vs. 8–14%); abdominal pain (16–23% vs. 11–19%); and diarrhoea (12–19% vs. 3–5%). The majority of AEs occurred within the first 24 h of treatment and proved transient.

Pooled results of the three Phase III studies show that serious AEs (SAEs) were reported in 2.7% of patients receiving the recommended dose of 2 mg (n = 661) vs. 2.0% of patients receiving placebo (n = 659). Discontinuation rates from AEs ranged from 4% to 15% among patients receiving prucalopride and from 2% to 7% among patients receiving placebo. Many discontinuations were the consequence of headache, abdominal pain, nausea, vomiting or diarrhoea which occurred on the first day of study drug administration.

Data from an open-label, long-term extension trial were recently reported. In this study, 1775 constipated patients who had completed one of the Phase III studies were followed up for a mean of 231 days (range 1–721 days). Similar to the Phase III trials, the most common AEs were headache (31%), abdominal pain (24%), diarrhoea (20%), flatulence (16%) and nausea (15%). The most common AE rated as ‘severe’ was surgical intervention (3.3%). SAEs were uncommon (<0.5%). The most common AEs leading to discontinuation were abdominal pain (1.5%) and headache (1.5%). Two deaths occurred; one was deemed unrelated to prucalopride and no treatment information was available for the other.

Unlike other 5-HT₄ receptor agonists, prucalopride has not been found to interact with the hERG channel or 5-HT₁(b) receptors, each postulated to be responsible for the development of adverse cardiovascular effects with other 5-HT₄ receptor agonists. Cardiovascular safety was evaluated in two Phase I, double-blind, controlled, two-way cross-over studies which included 32 and 24 healthy volunteers, in which prucalopride was escalated to a maximum dose of either 10 or 20 mg. No clinically relevant differences in blood pressure or incidence of prolonged QTc were identified between groups. Similarly, no correlation was found between observed shifts in ECG parameters based upon prucalopride concentrations up to 10 times the recommended therapeutic dose. A small, transient increase in mean heart rate and associated decrease in the PQ and QT intervals was observed with prucalopride. Within-subject differences between the groups were not statistically different. Cardiovascular safety was also carefully assessed in the Phase III clinical trials. There were no differences in vital signs or ECG parameters between study participants randomised to placebo or either dose of prucalopride. The incidence of QT interval prolongation (>470 ms) was low (≤ 2.1%) and similar between groups. A single cardiovascular event, an episode of supraventricular tachycardia, occurred in a patient with a history of mitral valve prolapse and cardiac arrhythmias, who was randomised to prucalopride 2 mg.

Cardiovascular safety was also assessed as part of a study conducted in a high-risk population. For this study, 89 elderly patients residing in a nursing facility (mean age 83 years) were randomised to prucalopride (0.5, 1 or 2 mg) or placebo. Of the participants, 80% had prior history of cardiovascular disease. There were no differences in vital signs, laboratory results or ECG parameters between groups. Moreover, there were no differences in the incidence of prolonged QTc interval between groups.

**Velusetrag (TD-5108).** Velusetrag is a high-affinity 5-HT₄ receptor agonist, which is being developed for the treatment of chronic constipation.
**Pharmacokinetics and pharmacodynamics.** The pharmacokinetics and pharmacodynamics of velusetrag are summarised in Tables 2 and 3 respectively.

**Clinical studies.** Clinical studies with velusetrag have focused on patients with chronic constipation. The few trials that have been published have described significant improvements in bowel frequency and constipation-related symptoms vs. placebo (Supplementary Table S7).

**Safety and tolerability.** In general, there were no SAEs with velusetrag treatment; notable AEs were the predictable GI effects such as diarrhoea or altered bowel movements. In the 401-patient Phase IIb trial, 12–15% of patients developed diarrhoea on velusetrag relative to placebo (1%). Of the three velusetrag doses tested, 15 mg provided the most favourable therapeutic index. The 50-mg dose was associated with higher prevalence of nausea, vomiting and headache than the other velusetrag doses and placebo.

An approximate 10 bpm increase in heart rate was observed following administration of 15 mg velusetrag in healthy volunteers and patients with chronic constipation. However, in the absence of a placebo control group, this observation is difficult to interpret. The significance of the single observations of palpitations (noted with velusetrag at 30 mg) and asymptomatic junctional escape rhythm (with 50 mg dose) noted in the pharmacodynamic transit study is uncertain, considering the limited number of subjects. In ~540 healthy subjects or patients with chronic constipation treated with velusetrag for up to 28 days, one patient with constipation experienced palpitations in the placebo group and one healthy volunteer had junctional escape rhythm following velusetrag at 70 mg.

In vitro studies show that velusetrag (3 μM, 5-min application, n = 3 cells) had no significant effect on the magnitude of hERG potassium tail currents recorded from Chinese hamster ovary (CHO)-K1 cells expressing hERG channels.

**Naronapride (ATI-7505).** Naronapride is structurally related to the chemical structure of cisapride, but devoid of significant affinities for other 5-HT receptors or the hERG channel. The drug is under evaluation for treatment of upper and lower GI motility disorders, but only limited data have been published.

**Clinical trials and indications/approvals.** Naronapride has been evaluated in Phase II trials in chronic constipation, GERD and FD. Naronapride (80 mg b.d.) demonstrated significant improvement over placebo in chronic constipation. In the upper GI tract, early Phase II studies indicated potential for reduction of reflux events and FD symptoms.

**Safety.** The cardiac safety of naronapride has been evaluated in a thorough QT study, which assesses the cardiac safety of a drug vs. both placebo and a positive control (e.g. moxifloxacin), and has confirmed a favourable safety profile at therapeutic or supratherapeutic doses.

**DISCUSSION**

Patients with symptoms that are potentially attributable to hypomotility of the GI tract constitute an important part of clinical GI practice. These conditions are part of a spectrum that ranges from functional dysphagia and GERD, through FD and gastroparesis, to IBS-C and chronic constipation. Prokinetic drugs are considered the drugs of choice for the treatment of hypomotility disorders, although the correlation between impaired motility and symptoms is inconsistent.

The 5-HT4 receptor, with its location on cholinergic nerve endings of interneurons and motor neurons, has been established as a valid target to enhance GI motility. Mechanistic studies have confirmed a stimulatory effect of 5-HT4 receptor agonists on GI motor activity, and clinical efficacy in hypomotility disorders has been established for a number of these drugs. Cisapride, as well as tegaserod, saw broad clinical application after regulatory approval (not in the EU for the latter drug), but both drugs were withdrawn (in the US), in part, because of cardiovascular AEs. The prevalence of cardiovascular AEs with both drugs was low and likely to fall below the limit of detection in a clinical trial programme.

These events might seriously hamper the clinical development of novel 5-HT4 receptor agonists for the treatment of GI hypomotility disorders, especially when taking into account the ability to establish cardiovascular safety. However, several chemical classes of 5-HT4 receptor agonists have been developed, and the selectivity of different compounds for the 5-HT4 receptor over other targets is highly variable between individual drugs and drug classes. The mechanism through which cisapride promotes cardiac arrhythmias is now clearly established to be unrelated to 5-HT4 receptor agonism. The cardiac risk associated with cisapride use is entirely attributable to its affinity for the hERG channel which results in QT
prolongation, and is enhanced by concomitant use of inhibitors of CYP, the principal pathway in cisapride metabolism.7, 8, 41, 59, 60, 62–69 Hence, 5-HT₄ receptor agonists without affinity for the hERG channel are devoid of this particular arrhythmogenic risk. Another risk factor in the case of cisapride was its metabolism through the CYP450 pathway, leading to increased plasma levels when other drugs also metabolised via this same pathway were taken at the same time. The mechanism through which tegaserod use may be associated with increased cardiovascular risk is not clearly established. However, it has been suggested that the affinity of tegaserod for the 5-HT₄ or 5-HT₂(b) receptors may underlie these AEs.27, 92 This would implicate lack of such risk for novel, highly-selective 5-HT₄ receptor agonists.

The link between cardiovascular risk, the CYP450 metabolic pathway and lack of selectivity of previously used 5-HT₄ receptor agonists supports the development of selective 5-HT₄ receptor agonists for the treatment of GI hypomotility disorders, as was the case with prucalopride for chronic constipation.27 The recent EMEA approval of prucalopride for the treatment of chronic constipation confirms that 5-HT₄ receptor agonists are still considered a valid therapeutic target at the regulatory level.1 Although no link between 5-HT₄ agonism and cardiovascular AEs has been established, standards for establishing cardiovascular safety for this class of drugs may still be elevated at the regulatory level. Indeed, the cardiovascular safety profile of prucalopride was assessed in great detail, both in vitro and in the clinical trial programme.26, 38, 130–132

Although this review may be limited by incomplete retrieval of relevant research, by bias in reporting such research, and by inherent risk of bias at the study level, our analysis of the literature has revealed a wealth of evidence that 5-HT₄ receptor agonists have clinical efficacy in the treatment of GI disorders and no evidence of cardiovascular safety concerns with selective 5-HT₄ receptor agonists. Nevertheless, caution is warranted as the number of patients exposed to the newer 5-HT₄ agonists is still relatively low (number of exposed patients can be derived from the Supplementary Tables for each drug), and adequate post-marketing surveillance will help to further establish the favourable cardiovascular risk profile of these agents.

CONCLUSIONS

5-HT₄ receptor agonists have clear-cut prokinetic effects in the gut. These agonists differ in many aspects that are either related or unrelated to their interaction with 5-HT₄ receptors. Differences that are unrelated to the 5-HT₄ receptor, such as affinity at non-5-HT₄ receptors, may influence the agent’s safety and overall benefit–risk profile. 5-HT₄ receptor-related differences have an impact on the agonists overall activity in a given tissue. Together, these differences affect the therapeutic potential for the treatment of GI motility disorders. Based on available evidence, a highly selective 5-HT₄ receptor agonist, such as prucalopride, may offer improved efficacy and safety to treat patients with impaired GI motility, such as severe chronic constipation.

ACKNOWLEDGEMENTS

Declaration of personal interests: Jan Tack has served as a scientific advisor for Addex pharma, AGI Therapeutics, Almirall, Aryx, AstraZeneca, Danone, Ipsen, Menarini, Movetis, Norgine, Novartis, Nycomed, Ocera, Rose Pharma, SK Life Sciences, Smartpill, Sucampo, Theravance, Tranzyme, Xenopoint and Zeria, and a speaker for Abbott, AstraZeneca, Menarini, Movetis, Novartis and Nycomed. Michael Camilleri has served as a consultant and an advisory board member for Adolor, Albireo Pharma, Alkermes, Ardelyx, ARYx Therapeutics, Ascent, Astellas, AstraZeneca, BioKier, Biomedical Insights, Domain, GlaxoSmitKline, Ikaria, Ironwood, Johnson & Johnson, NovaSecta, Ocura, Procter & Gamble, Shire, SK Bio, Synergy, Takeda, Theravance and Tranzyme, and has received research funding from Alibero, NIH, Rose Pharma, Tsunura and Wyeth. Lin Chang has served as a consultant or an advisory board member for Prometheus Laboratories, Takeda, Albireo, Rose Pharma, GlaxoSmithKline, Ironwood, Forest, Salix, Marathon Pharmaceuticals, Novo Nordisk, Lexicon and Movetis, and has received research funding from Prometheus, Rose Pharma, Takeda, Ironwood and Shire. William D. Chey has served as a consultant and an advisory board member for Albireo, AstraZeneca, Forest, Ironwood, Procter & Gamble, Prometheus, Salix, Smartpill, Takeda, and has received research funding from Ardelyx and Ironwood. James J. Galligan has served as a consultant for Faegre and Benson (now Faegre, Baker, Daniels), and LLP. Brian E. Lacy has served as a speaker for Novartis, Prometheus and Takeda, and an advisory board member for Prometheus, Takeda, Ironwood and Movetis. Dr Lacy has received investigator-initiated, unrestricted funding from Takeda. Stefan Müller-Lissner has served as a speaker, a consultant and an advisory board member for Axcan, Boehringer Ingelheim, Falk Foundation, Janssen, Movetis, Menarini Farmaceutica, Movetis, Mundipharma GmbH, Novartis, Pfizer, Procter & Gamble, Sucampo Pharma and Zeria Pharma. Eamonn M. M. Quigley has served as a consultant and an advisory board member for Movetis. Dr Quigley has also served as an advisory board chair for Janssen. Jan Schuur-
J. Tack et al.

kes is an employee of Shire. Joris H. De Maeyer is an employee of Shire. Vincenzo Stanghellini has served as speaker and advisory board member for Axcan, Danone, Janssen, Movetis, Nycomed, Norgine, Novartis, Pfizer, Sofar and Valeas. Declaration of funding interests: The writing or preparation of this paper was funded in part by Movetis; writing support (conducting searches and editing the manuscript) was provided by Kate Carpenter and Victoria Harvey of Choice Pharma, and was funded by Movetis.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical trials on the efficacy of cisapride in GI conditions.
Table S2. Clinical trials on the efficacy of tegaserod in GI conditions.

REFERENCES

1. Sanger GJ, Alpers DH. Development of drugs for gastrointestinal motor disorders: translating science to clinical need. Neurogastroenterol Motil 2008; 20: 177–84.
2. Briejer MR, Akkermans LM, Schuurkes JA. Gastrointestinal prokinetic benzamides: the pharmacology underlying stimulation of motility. Pharmacol Rev 1995; 47: 631–51.
3. Langlois M, Fischmeister R. 5-HT4 receptor ligands: applications and new prospects. J Med Chem 2003; 46: 319–44.
4. Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Cochrane Database Syst Rev 2007; CD003960.
5. McCallum RW, Prakash C, Campoli-Richards DM, Goa KL. Cisapride. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use as a prokinetic agent in gastrointestinal motility disorders. Drugs 1988; 36: 652–81.
6. Novartis. Press release: Novartis suspends US marketing and sales of Zelnorm in response to request from FDA. Available at: http://hugin.info/134323/R/1116336/204121.pdf. Accessed December 14, 2010.
7. Drolet B, Khalifa M, Daleau P, Hamelin BA, Turgeon J. Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies drug-related lengthening of the QT interval. Circulation 1998; 97: 204–10.
8. Jones JK, Fife D, Curkendall S, Goehring E Jr, Guo JJ, Shannon M. Coprescribing and codispensing of cisapride and contraindicated drugs. JAMA 2001; 286: 1607–9.
9. US Food & Drug Administration. Zelnorm (tegaserod maleate). April 2009. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm. Accessed December 14, 2010.
10. Department of Health. Medicines Control Agency announces withdrawal of Cisapride July 2000. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Pressreleases/DH_4005066. Accessed December 14, 2010.
11. Dumuis A, Sebben M, Bockaert J. The gastrointestinal prokinetic benzamide derivatives are agonists at the non-classical 5-HT receptor (5-HT4) positively coupled to adenylyl cyclase in neurons. Naunyn Schmiedebergs Arch Pharmacol 1989; 340: 403–10.
12. Markstein R, Matsumoto M, Kohler C, Togashi H, Yoshioka M, Hoyer D. Pharmacological characterisation of 5-HT receptors positively coupled to adenylyl cyclase in the rat hippocampus. Naunyn Schmiedebergs Arch Pharmacol 1999; 359: 454–9.
13. Blondel O, Gastineau M, Dahmoune Y, Langlois M, Fischmeister R. Cloning, expression, and pharmacology of four human 5-hydroxytryptamine 4 receptor isoforms produced by alternative splicing in the carboxyl terminus. J Neurochem 1998; 70: 2252–61.
14. Medhurst AD, Lezoualch F, Fischmeister R, Middlemiss DN, Sanger GJ. Quantitative mRNA analysis of five C-terminal splice variants of the human 5-HT4 receptor in the central nervous system by TaqMan real time RT-PCR. Brain Res Mol Brain Res 2001; 90: 125–34.
15. Claeyssen S, Faye P, Sebben M, Taviaux S, Bockaert J, Dumuis A. 5-HT4 receptors: cloning and expression of new splice variants. Ann N Y Acad Sci 1998; 861: 49–56.
16. Ray AM, Kellsel RE, Houp JA, et al. Identification of a novel 5-HT(4) receptor splice variant (5-HT(4)e1) and preliminary characterisation of specific 5-HT(4a) and 5-HT(4b) receptor antibodies. Eur J Pharmacol 2009; 604: 1–11.
17. De Maeyer JH, Aersens J, Verhasselt P, Lefebvre RA. Alternative splicing and exon duplication generates 10 unique porcine 5-HT 4 receptor splice variants including a functional homofusion variant. Physiol Genomics 2008; 34: 22–33.
18. Bender E, Pindon A, van Oers I, et al. Structure of the human serotonin 5-
HT4 receptor gene and cloning of a novel 5-HT4 splice variant. *J Neurochem* 2000; 74: 478–89.

19. Claeyssen S, Sebben M, Becamel C, Bockaert J, Dumuis A. Novel brain-specific 5-HT4 receptor splice variants show marked constitutive activity: role of the C-terminal intracellular domain. *Mol Pharmacol* 1999; 55: 910–20.

20. Liu M, Geddis MS, Wen Y, Setlik W, Gershon MD. Expression and function of 5-HT4 receptors in the mouse enteric nervous system. *Am J Physiol Gastrointest Liver Physiol* 2005; 289: G1148–63.

21. van Leersveld N, Ter Linde J, Schipper M, Sanssom M. Serotonergic signalling in the stomach and duodenum of patients with gastroparesis. *Neurogastroenterol Motil* 2008; 20: 148–55.

22. Matsumoto M, Togashi H, Mori K, et al. Evidence for involvement of central 5-HT(4) receptors in cholinergic function associated with cognitive processes: behavioral, electrophysiological, and neurochemical studies. *J Pharmacol Exp Ther* 2001; 296: 676–82.

23. Yan Z. Regulation of GABAergic inhibition by serotonin signaling in prefrontal cortex: molecular mechanisms and functional implications. *Mol Neurobiol* 2002; 26: 203–16.

24. Alex KD, Pehek EA. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacol Ther* 2007; 113: 296–320.

25. Brattelid T, Qvigstad E, Lynham JA, et al. Characterization of 5-HT3 and ‘atypical’ 5-HT receptors mediating guinea-pig ileal contractions in vitro. *Br J Pharmacol* 1990; 101: 513–20.

26. Kilbinger H, Gebauer A, Haas J, Ladinsky H, Rizzi CA. Benzimidazolones and renzapride facilitate acetylcholine release from guinea-pig myenteric plexus via 5-HT4 receptors. *Naunyn Schmiedebergs Arch Pharmacol* 1995; 351: 229–36.

27. Kilbinger H, Wolf D. Effects of 5-HT4 receptor stimulation on basal and electrically evoked release of acetylcholine from guinea-pig myenteric plexus. *Naunyn Schmiedebergs Arch Pharmacol* 1992; 345: 270–5.

28. Pan H, Galligan J. 5-HT1A and 5-HT4 receptors mediate inhibition and facilitation of fast synaptic transmission in enteric neurons. *Am J Physiol* 1994; 266: G230–8.

29. Ren J, Zhou X, Galligan JJ. 5-HT4 receptor activation facilitates recovery from synaptic rundown and increases transmitter release from single varicosities of myenteric neurons. *Am J Physiol Gastrointest Liver Physiol* 2008; 294: G1376–83.

30. Leclere PG, Lefebvre RA. Presynaptic modulation of cholinergic neurotransmission in the human proximal stomach. *Br J Pharmacol* 2002; 135: 43–52.

31. Leclere PG, Prins NH, Schuurkes JA, Lefebvre RA. 5-HT4 receptors located on cholinergic nerves in human colon circular muscle. *Neurogastroenterol Motil* 2005; 17: 366–75.

32. De Maeyer JH, Schuurkes JA, Lefebvre RA. Selective desensitization of the 5-HT4 receptor-mediated response in pig atrium but not in stomach. *Br J Pharmacol* 2009; 156: 362–76.

33. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. *Neurogastroenterol Motil* 2008; 20: 99–112.

34. Baxter GS, Craig DA, Clarke DE. 5-Hydroxytryptamine(1) receptors mediate relaxation of the rat oesophageal tunica muscularis mucosae. *Naunyn Schmiedebergs Arch Pharmacol* 1991; 343: 439–466.

35. Prins NH, Van Haselen JP, Lefebvre RA, Briejer MR, Akkermans LM, Schuurkes JA. Pharmacological characterization of 5-HT4 receptors mediating relaxation of canine isolated rectum circular smooth muscle. *Br J Pharmacol* 1999; 127: 1431–7.

36. Prins NH, Shankley NP, Welsh NJ, et al. An improved in vitro bioassay for the study of 5-HT(4) receptors in the human isolated large intestinal circular muscle. *Br J Pharmacol* 2000; 129: 1601–8.

37. Eglen RM, Swank SR, Walsh LK, Whiting RL. Characterization of 5-HT3 and ‘atypical’ 5-HT receptors mediating guinea-pig ileal contractions in vitro. *Br J Pharmacol* 1999; 101: 513–20.

38. Kilbinger H, Gebauer A, Haas J, Ladinsky H, Rizzi CA. Benzimidazolones and renzapride facilitate acetylcholine release from guinea-pig myenteric plexus via 5-HT4 receptors. *Naunyn Schmiedebergs Arch Pharmacol* 1995; 351: 229–36.

39. Kilbinger H, Wolf D. Effects of 5-HT4 receptor stimulation on basal and electrically evoked release of acetylcholine from guinea-pig myenteric plexus. *Naunyn Schmiedebergs Arch Pharmacol* 1992; 345: 270–5.

40. Pan H, Galligan J. 5-HT1A and 5-HT4 receptors mediate inhibition and facilitation of fast synaptic transmission in enteric neurons. *Am J Physiol* 1994; 266: G230–8.

41. Ren J, Zhou X, Galligan JJ. 5-HT4 receptor activation facilitates recovery from synaptic rundown and increases transmitter release from single varicosities of myenteric neurons. *Am J Physiol Gastrointest Liver Physiol* 2008; 294: G1376–83.

42. Leclere PG, Lefebvre RA. Presynaptic modulation of cholinergic neurotransmission in the human proximal stomach. *Br J Pharmacol* 2002; 135: 43–52.

43. Leclere PG, Prins NH, Schuurkes JA, Lefebvre RA. 5-HT4 receptors located on cholinergic nerves in human colon circular muscle. *Neurogastroenterol Motil* 2005; 17: 366–75.

44. De Maeyer JH, Prins NH, Schuurkes JA, Lefebvre RA. Differential effects of 5-hydroxytryptamine4 receptor agonists at gastric versus cardiac receptors: an operational framework to explain and quantify organ-specific behavior. *J Pharmacol Exp Ther* 2006; 317: 955–64.

45. Potet F, Bouyssou T, Escande D, Baro et al. Gastrointestinal prokinetic drugs have different affinity for the human cardiac human ether-a-go-go K(+) channel. *J Pharmacol Exp Ther* 2001; 299: 1007–12.

46. Nagakura Y, Akuzawa S, Miyata K, et al. Pharmacological properties of a novel gastrointestinal prokinetic benzamide selective for human 5-HT4 receptor versus human 5-HT3 receptor. *Pharmacol Res* 1999; 39: 375–82.

47. Mohammad S, Zhou Z, Gong Q, January CT. Blockage of the HERG human cardiac K+ channel by the gastrointestinal prokinetic agent cisapride. *Am J Physiol* 1997; 273: H2534–4.

48. Mine Y, Yoshikawa T, Oku S, Nagai R, Yoshida N, Hosoki K. Comparison of effect of mosapride citrate and existing 5-HT4 receptor agonists on gastrointestinal motility in vivo and in vitro. *J Pharmacol Exp Ther* 1997; 283: 1000–8.

49. Wardle KA, Sanger GJ. The guinea-pig distal colon–a sensitive preparation for the investigation of 5-HT4 receptor-mediated contractions. *Br J Pharmacol* 1993; 110: 1593–9.

50. Camilleri M, Vazquez-Roque ML, Burton D, et al. Pharmacodynamic effects of a novel prokinetic 5-HT4 receptor agonist, AT1-7505, in humans. *Neurogastroenterol Motil* 2007; 19: 30–8.

51. Dennis D, Palme M, Irwin I, Druzhala P, Teichman S. AT1-7505 is a novel, selective 5HT(4) receptor agonist that causes gastrointestinal prokinetic activity in dogs. *Gastroenterology* 2004; 126: A641.

52. Beattie DT, Smith JA, Marquess D, et al. The 5-HT4 receptor agonist, tegaserod, is a potent 5-HT2B receptor antagonist in vitro and in vivo. *Br J Pharmacol* 2004; 143: 549–60.

53. McCellough JL, Armstrong SR, Hegde SS, Beattie DT. The 5-HT2B antagonist and 5-HT4 agonist activities of tegaserod in the anaesthetized rat. *Pharm Res* 2006; 53: 353–8.

54. Graider JR, Foxx-Orenstein AE, Jin JG. 5-Hydroxytryptamine4 receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. *Gastroenterology* 1998; 115: 370–80.

55. Buchheit KH, Gamse R, Giger R, et al. The serotonin 5-HT4 receptor. 2. Structure–activity studies of the indole carbazimidamide class of agonists. *J Med Chem* 1995; 38: 2331–8.

56. Buchheit KH, Gamse R, Giger R, et al. The serotonin 5-HT4 receptor. 1. Design of a new class of agonists and receptor map of the agonist recognition site. *J Med Chem* 1995; 38: 2326–30.

57. Emmanouel AV, Kamm MA, Roy AJ, Antonelli K. Effect of a novel prokinetic drug, R093877, on gastrointestinal transit in healthy volunteers. *Gut* 1998; 42: 511–6.

58. Briejer MR, Prins NH, Schuurkes JA. Effects of the enterokinetic
prucalopride (R093877) on colonic motility in fasted dogs. *Neurogastroenterol Motil* 2001; 13: 465–72.

53. Bouras E, Camelier M, Burton DD, McKinzie S. Selective stimulation of colonic transit by the benzofuran 5HT4 agonist, prucalopride, in healthy humans. *Gut* 1999; 44: 682–6.

54. Briejer MR, Bosmans JP, Van Daele P, et al. The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound. *Eur J Pharmacol* 2001; 423: 71–83.

55. Smith JA, Beattie DT, Marquess D, Shaw JP, Vickery RG, Humphrey PP. The in vitro pharmacological profile of TD-5108, a selective 5-HT(4) receptor agonist with high intrinsic activity. *Naunyn Schmiedebergs Arch Pharmacol* 2008; 378: 125–37.

56. Beattie DT, Armstrong SR, Shaw JP, et al. The in vivo gastrointestinal activity of TD-5108, a selective 5-HT(4) receptor agonist with high intrinsic activity. *Naunyn Schmiedebergs Arch Pharmacol* 2008; 378: 139–47.

57. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. *Aliment Pharmacol Ther* 2010; 31: 1–9.

58. Wager E, Tooley PJ, Pearce GL, Wilton LV, Mann RD. A comparison of two cohort studies evaluating the safety of cisapride: Prescription-Event Monitoring and a large phase IV study. *Eur J Clin Pharmacol* 1997; 52: 87–94.

59. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med* 1999; 107: 356–62.

60. B ley J, Hayes C, Kern J, et al. Does cisapride influence cardiac rhythm? Results of a United States multicenter, double-blind, placebo-controlled pediatric study. *J Pediatr Gastroenterol Nutr* 2001; 32: 458–63.

61. Dalby-Payne JR, Morris AM, Craig JC. Meta-analysis of randomized controlled trials on the benefits and risks of using cisapride for the treatment of gastroesophageal reflux in children. *J Gastroenterol Hepatol* 2003; 18: 196–202.

62. Olsson S, Edwards IR. Tachycardia during cisapride treatment. BMJ 1992; 305: 748–9.

63. Snalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of food and drug administration regulatory action. *JAMA* 2000; 284: 3036–9.

64. Gross AS, Goh YD, Addison RS, Shenfield GM. Influence of grapefruit juice on cisapride pharmacokinetics. *Clin Pharmacol Ther* 1999; 65: 395–401.

65. Hancock JC, James AF. Refining insights into high-affinity drug binding to the human ether-a-go-go-related gene potassium channel. *Mol Pharmacol* 2008; 73: 1592–5.

66. Di Diego JM, Belardinelli L, Antzelevitch C. Cisapride-induced transmural dispersion of repolarization and torsade de points in the canine left ventricular wedge preparation during epicardial stimulation. *Circulation* 2003; 108: 1027–33.

67. Chhina S, Pereverin RL, Deming DD, Hopper AO, Hashmi A, Vyhmeister NR. QTc interval in infants receiving cisapride. *J Perinatol* 2002; 22: 144–8.

68. Treluyer JM, Rey E, Sonnir M, Pons G, Cresteil T. Evidence of impaired cisapride metabolism in neonates. *Br J Clin Pharmacol* 2001; 52: 419–25.

69. Cools F, Benatar A, Bruneel E, et al. A comparison of the pharmacokinetics of two dosing regimens of cisapride and their effects on corrected QT interval in premature infants. *Eur J Clin Pharmacol* 2003; 59: 17–22.

70. Kyrmizakis DE, Chimona TS, Kanouparis EM, Papadakis CE, Vegarakis GA, Helidonis ES. QT prolongation and torsades de pointes associated with concurrent use of cisapride and erythromycin. *Am J Otolaryngol* 2002; 23: 303–7.

71. Evans AJ, Krentz AJ. Should cisapride be avoided in patients with diabetic gastroparesis? *J Diabetes Complications* 1999; 13: 314–5.

72. Gray VS. Syncopal episodes associated with metoclopramide and concurrent drugs. *Ann Pharmacother* 1998; 32: 648–51.

73. Hatlebakk JG, Johnsson F, Vilien M, et al. The effect of cisapride in maintaining symptomatic remission in patients with gastro-oesophageal reflux disease. *Scand J Gastroenterol* 1997; 32: 1100–6.

74. Lander A, Redkar R, Nicholls G, et al. Cisapride reduces neonatal postoperative ileus: randomised placebo controlled trial. *Arch Dis Child Fetal Neonatal Ed* 1997; 77: F119–22.

75. Muller-Lissner SA. Treatment of chronic constipation with cisapride and placebo. *Gut* 1987; 28: 1033–8.

76. Nurko S, Garcia-Aranda JA, Worona LB, Zlochisty O. Cisapride for the treatment of constipation in children: A double-blind study. *J Pediatr* 2000; 136: 35–40.

77. Tack J, Muller-Lissner S. Treatment of chronic constipation: current pharmacologic approaches and future directions. *Clin Gastroenterol Hepatol* 2009; 7: 502–8.

78. Quigley EM, Wald A, Fidelholtz J, Boivin M, Pecher E, Earnest D. Safety and tolerability of tegaserod in patients with chronic constipation: pooled data from two phase III studies. *Clin Gastroenterol Hepatol* 2006; 4: 605–13.

79. Fock-Kwong M, Wagner A. Safety, tolerability and satisfaction with tegaserod therapy in Asia-Pacific patients with irritable bowel syndrome with constipation. *J Gastroenterol Hepatol* 2007; 22: 1190–8.

80. Fried M, Beglinger C, Bobalj NG, Minor N, Coello N, Michetti P. Tegaserod is safe, well tolerated and effective in the treatment of patients with non-diarrhoea irritable bowel syndrome. *Eur J Gastroenterol Hepatol* 2005; 17: 421–7.

81. Tougas G, Snape WJ Jr, Otten MH, et al. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2002; 16: 1701–8.

82. Muller-Lissner S, Kamm MA, Musoglu A, Earnest DL, Dunger-Baldauf C, Shetzel MA. Safety, tolerability, and efficacy of tegaserod over 13 months in patients with chronic constipation. *Am J Gastroenterol* 2006; 101: 2558–69.

83. Schoenfeld P. Systematic review: incidence of abdominal/pelvic surgery amongst patients using tegaserod in randomized controlled trials. *Aliment Pharmacol Ther* 2004; 19: 263–9.

84. Singh G, Mithal A, Kahler K, Shetzel M, Triadalopoulus G. Patients with irritable bowel syndrome have a high risk of developing colon ischemia [abstract]. *Gut* 2004; 53(Suppl. VI): A66.

85. Joelsson B, Shetzel MA, Cunningham S. Tegaserod and ischemic colitis. *New Engl J Med* 2004; 351: 1363.

86. Brinker AD, Mackey AC, Prizont R. Tegaserod and ischemic colitis. *N Engl J Med* 2004; 351: 1361–4.

87. DiBaise JK. Tegaserod-associated ischemic colitis. *Pharmacotherapy* 2005; 25: 620–5.

88. Woolorton E, Tegaserod (Zelnorm) for irritable bowel syndrome: reports of serious diarrhea and intestinal ischemia. *CMAJ* 2004; 170: 1908.

89. Higgins PD, Davis KJ, Laine L. Systematic review: the epidemiology of ischemic colitis. *Aliment Pharmacol Ther* 2004; 19: 729–38.

90. Morganroth J, Ruegg PC, Dunger-Baldauf C, Appel-Dingemanse S, Bliesath H, Lefkowitz M. Tegaserod, a 5-hydroxytryptamine type 4 receptor partial agonist, is devoid of
constipation. N Engl J Med 2008; 358: 2344–54.

126. Emmanuel AV, Roy AJ, Nicholls TJ, Kamm MA. Prucalopride, a systemic enterokinetic, for the treatment of constipation. Aliment Pharmacol Ther 2002; 16: 1347–56.

127. Quigley EM, Vandeplasse L, Kerstens R, Ausma J. 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 2009; 29: 315–28.

128. Tack J, van Outryve M, Beyens G, Kerstens R, Vandeplasse L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut 2009; 58: 357–65.

129. Tack J, Ausma J, Kerstens R, Vandeplasse L. Safety and tolerability of prucalopride (Resolor®) in patients with chronic constipation: Pooled data from three pivotal phase III studies [Abstract T1322]. Gastroenterology 2008; 134: A530–1.

130. Camilleri M, Beyens G, Kerstens R, Vandeplasse L. Long-term follow-up of safety and satisfaction with bowel function in response to oral prucalopride in patients with chronic constipation [Abstract]. Gastroenterology 2009; 136(Suppl. 1): 160.

131. Boyce M, Kerstens R, Beyens G, Ausma J, Vandeplasse L. Cardiovascular safety of prucalopride in healthy subjects: results from two randomized, double-blind, placebo-controlled, cross-over trials [Abstract]. Gastroenterology 2009; 136(Suppl. 1): T1265.

132. Camilleri M, Kerstens R, Beyens G, Robinson P, Vandeplasse L. A double-blind, placebo-controlled trial to evaluate the safety and tolerability of prucalopride oral solution in constipated elderly patients living in a nursing facility [Abstract]. Gastroenterology 2009; 136(Suppl. 1): 240.

133. Goldberg MR, Li YP, Pitzer K, Johanson JF, Mangel A, Kitt MM. TD-5108 a selective 5-HT4 receptor agonist, is consistently better than placebo regardless of response definition in patients with chronic constipation. Gastroenterology 2008; 134: A547.

134. Manini ML, Camilleri M, Goldberg M, et al. Effects of velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation. Neurogastroenterol Motil 2010; 22: 42–9.

135. Theravance. Data on file.

136. Dennis D, Palme M, Irwin I, Druzgala P, Teichman S. ATI-7505 is a novel, selective 5HT(4) receptor agonist that causes gastrointestinal prokinetic activity in dogs. Gastroenterology 2004; 126: A641.

137. Palme M, Milner PG, Ellis DJ, Marmon T, Canafax DM. A Novel Gastrointestinal Prokinetic, ATI-7505, Increased Spontaneous Bowel Movements (Smhs) in a Phase II, Randomized, Placebo-Controlled Study of Patients With Chronic Idiopathic Constipation (CIC). Gastroenterology 2010; 138: S128–9.

138. Aryx Therapeutics. ATI-7505 product fact sheet.

139. Aryx Therapeutics. ATI-7505 – Gastrointestinal Disorders. Addressing safety, impact on quality of life, and pharmacokinetics of SDZ HTF 919, a novel selective 5-HT4 receptor agonist, following oral and intravenous administration. Br J Clin Pharmacol 1999; 47: 483–91.

140. Yamamoto T, Takano K, Sanaka M, et al. Pharmacokinetic characteristics of cisapride in elderly patients. Int J Clin Pharmacol Ther 1998; 36: 432–4.

141. Appel-Dingemanse S, Lemarechal MO, Mechlinski W, Pesco-Koplowitz L. Pharmacokinetic profile of cisapride 20 mg after once- and twice-daily dosing. Clin Ther 1998; 20: 292–8.

142. Yamamoto T, Takano K, Sanaka M, et al. Pharmacokinetic characteristics of cisapride in elderly patients. Int J Clin Pharmacol Ther 1998; 36: 432–4.

143. Appel-Dingemanse S, Lemarechal MO, Mechlinski W, Hubert M, Legangneux E. Integrated modelling of the clinical pharmacokinetics of SDZ HTF 919, a novel selective 5-HT4 receptor agonist, following oral and intravenous administration. Br J Clin Pharmacol 1999; 47: 483–91.

144. Mims USA. Zelnorm - Detailed prescribing information. Available at: http://www.mims.com/USA/drug/info/ Zelnorm/Zelnorm%20Tablet? q=tadagra&type=full. Accessed December 8, 2011.

145. Achtgert G, Borchers F, Finner E, Hausleiter HJ. Metabolism of cisapride in animals and man. In: Poster presented at the 12th European Workshop on Drug Metabolism; 1990; Basel, Switzerland; 1990.

146. Sakashita M, Mizuki Y, Yamaguchi T, Miyazaki H, Sekine Y. Pharmacokinetics of the gastrokinetic agent mosapride citrate after intravenous and oral administrations in dogs and monkeys. Arzneimittelforschung 1993; 43: 864–6.

147. Sakashita M, Yamaguchi T, Miyazaki H, et al. Pharmacokinetics of the gastrokinetic agent mosapride citrate after single and multiple oral administrations in healthy subjects. Arzneimittelforschung 1993; 43: 867–72.

148. Dianippon Pharma. Mosapride package insert.

149. Bhan CS, Saraswat R. Short review of mosapride: a prokinetic agent. Journal of Global Pharma Technology 2011; 3: 1–4.

150. Shire-Movets. Resolor (prucalopride) Summary of product characteristics. October 2009. Available at: http://www.medicines.org.uk/EMC/history/ 23206/SPC/Resolor+2mg+film-coated +tablets#03/02/2012 to Current.

151. Bowersox SS, Lightning KJ, Rao S, et al. Metabolism and pharmacokinetics of naronapride (ATI-7505), a serotonin 5-HT(4) receptor agonist for gastrointestinal motility disorders. Drug Metab Dispos 2011; 39: 1170–80.
158. Chen SD, Kao CH, Chang CS, Chen GH. Salivary function in patients with reflux esophagitis: effect of cisapride. *J Nucl Med* 1998; 39: 1449–52.

159. Orr WC, Chen CL, Sloan S. The role of age and salivation in acid clearance in symptomatic patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2001; 15: 1385–8.

160. Ceccatelli P, Janssens J, Vantrappen G, Cucchiara S. Cisapride restores the decreased lower oesophageal sphincter pressure in reflux patients. *Gut* 1988; 29: 631–5.

161. Corazziari E, Bontempo I, Anzini F. Effects of cisapride on distal oesophageal motility in humans. *Dig Dis Sci* 1989; 34: 1600–5.

162. Cucchiara S, Staiano A, Bocciari A, *et al*. Effects of cisapride on parameters of oesophageal motility and on the prolonged intraoesophageal pH test in infants with gastro-oesophageal reflux disease. *Gut* 1990; 31: 21–5.

163. Paterson WG, Wang H, Beck IT. The effect of cisapride in patients with reflux esophagitis: an ambulatory oesophageal manometry/pH-metry study. *Am J Gastroenterol* 1997; 92: 226–30.

164. Horowitz M, Maddox A, Harding PE, *et al*. Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. *Gastroenterology* 1987; 92: 1899–907.

165. Gardner JD, Rodriguez-Stanley S, Robinson M, Miner PB, Jr. Cisapride inhibits meal-stimulated gastric acid secretion and post-prandial gastric acidity in subjects with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2002; 16: 1819–29.

166. Inauen W, Emde C, Weber B, *et al*. Effects of ranitidine and cisapride on acid reflux and oesophageal motility in patients with reflux oesophagitis: a 24 hour ambulatory combined pH and manometry study. *Gut* 1993; 34: 1025–31.

167. Katschinski M, Schirra J, Arnold R. The efficacy of a 40-mg extended-release formulation of cisapride in the treatment of patients with gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2000; 14: 113–22.

168. Pouseroux P, Kahrilas PJ. A comparative study of cisapride and ranitidine at controlling oesophageal acid exposure in erosive oesophagitis. *Aliment Pharmacol Ther* 1995; 9: 661–6.

169. Gilbert RJ, Dodds WJ, Kahrilas PJ, Hogan WJ, Lipman S. Effect of cisapride, a new prokinetic agent, on oesophageal motor function. *Dig Dis Sci* 1987; 32: 1331–6.

170. Smout AJ, Bogaard JW, Grade AC, ten Thije OJ, Akkermans LM, Wittebol P. Effects of cisapride, a new gastrointestinal prokinetic substance, on interdigestive and postprandial motor activity of the distal oesophagus in man. *Gut* 1983; 26: 246–51.

171. Degen L, Petrig C, Studer D, Schroller S, Beglinger C. Effect of tegaserod on gut transit in male and female subjects. *Neu gastroenterol Motil* 2005; 17: 821–6.

172. Harish K, Hazeeka K, Thomas V, Kumar S, Jose T, Narayanan P. Effect of tegaserod on colonic transit time in male patients with constipation–predominant irritable bowel syndrome. *J Gastroenterol Hepatol* 2007; 22: 1183–9.

173. Bovero E, Poletti M, Vigneri S. The effect of clebopride on oesophageal motility: a double-blind randomized manometric study. *Carr Ther Res* 1989; 46: 895–901.

174. Ruth M, Finizia C, Cange L, Lundell L. The effect of mosapride on oesophageal motor function and acid reflux in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2003; 15: 1115–21.

175. Ruth M, Hamelin B, Rohss K, Lundell L. The effect of mosapride, a novel prokinetic, on acid reflux variables in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1998; 12: 35–40.

176. Wallin L, Kruse-Andersen S, Madsen T, Boesby S. Effect of cisapride on the gastro-oesophageal function in normal human subjects. *Digestion* 1987; 37: 160–5.

177. Finizia C, Lundell L, Cange L, Ruth M. The effect of cisapride on oesophageal motility and lower sphincter function in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2003; 15: 9–14.

178. Cho YK, Choi MG, Han HW, *et al*. The effect of mosapride on oesophageal motility and bolus transit in asymptomatic volunteers. *J Clin Gastroenterol* 2006; 40: 286–92.

179. Vantrappen G, Corton P, Janssens J. The effect of clebopride on lower oesophageal sphincter pressure in normal subjects. *Carr Ther Res* 1985; 37: 284–95.

180. Pehlivanov N, Sarosiek I, Whitman R, Olyae G, McCallum R. Effect of cisapride on nocturnal transient lower oesophageal sphincter relaxations and nocturnal gastro-oesophageal reflux in patients with oesophagitis: a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2002; 16: 743–7.

181. Holloway RH, Downton J, Mitchell B, Dent J. Effect of cisapride on postprandial gastro-oesophageal reflux. *Gut* 1989; 30: 1187–93.

182. Smythe A, Bird NC, Trey GP, Ackroyd R, Johnson AG. Does the addition of a prokinetic to proton pump inhibitor therapy help reduce duodenogastric–oesophageal reflux in patients with Barrett’s oesophagus? *Eur J Gastroenterol Hepatol* 2003; 15: 305–12.

183. Chen JD, Ke MY, Lin XM, Wang Z, Zhang M. Cisapride provides symptomatic relief in functional dyspepsia associated with gastric myoelectrical abnormality. *Aliment Pharmacol Ther* 2000; 14: 1041–7.

184. Besherdas K, Leahy A, Mason I, Harbord M, Epstein O. The effect of cisapride on dyspepsia symptoms and the electrogastrogram in patients with non-ulcer dyspepsia. *Aliment Pharmacol Ther* 1998; 12: 755–9.

185. Borovicka J, Lehmann R, Kunz P, *et al*. Evaluation of gastric emptying and motility in diabetic gastroparesis with magnetic resonance imaging: effects of cisapride. *Am J Gastroenterol* 1999; 94: 2866–73.

186. Jones KL, Horowitz M, Carney BI, Sun WM, Chatterton BE. Effects of cisapride on gastric emptying of oil and aqueous meal components, hunger, and fullness. *Gut* 1996; 38: 310–5.

187. Lazzaroni M, Sangaletti O, Bianchi Porro G. Effect of cisapride on gastric emptying and ileal transit time of balanced liquid meal in healthy subjects. *Digestion* 1987; 37: 110–3.

188. Fraser RJ, Horowitz M, Maddox AF, Dent J. Postprandial antropyloroduodenal motility and gastric emptying in gastroparesis – effects of cisapride. *Gut* 1994; 35: 172–8.

189. Stacher G, Granser CV, Bergmann H, Kugi A, Stacher-Janotta G, Hobart J. Slow gastric emptying induced by high fat content of meal accelerated by cisapride administered rectally. *Dig Dis Sci* 1991; 36: 1259–65.

190. Camilleri M, Malagelada JR, Abell TL, Brown ML, HENCH V, Zinsmeister AR. Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. *Gastroenterology* 1989; 96: 704–12.

191. Jian R, Ducrot F, Piedeloup C, Mary JY, Najean Y, Bernier JI. Measurement of gastric emptying in dyspeptic patients: effect of a new gastrokinetic agent (cisapride). *Gut* 1985; 26: 352–8.
192. Feldman M, Smith HJ. Effect of cisapride on gastric emptying of indigestible solids in patients with gastroparesis diabeticorum. A comparison with metoclopramide and placebo. *Gastroenterology* 1987; 92: 171–4.

193. Kawagishi T, Nishizawa Y, Okuno Y, Morii H. Effect of cisapride on gastric emptying of indigestible solids and plasma motilin concentration in diabetic autonomic neuropathy. *Am J Gastroenterol* 1993; 88: 933–8.

194. Richards RD, Valenzuela GA, Davenport KG, Fisher KL, McCallum RW. Objective and subjective results of a randomized, double-blind, placebo-controlled trial using cisapride to treat gastroparesis. *Dig Dis Sci* 1993; 38: 811–6.

195. Corinaldesi R, Stanghellini V, Raiti C, Richards RD, Valenzuela GA, Sekiya K, Morii H. Effect of cisapride on gastric emptying of a solid meal and on dyspeptic symptoms in patients with idiopathic gastroparesis. *Gut* 1987; 28: 300–5.

196. Abell TL, Camilleri M, DiMagno EP, Hench VS, Zinsmeister AR, Malagelada JR. Long-term efficacy of oral cisapride in symptomatic upper gut dysmotility. *Dig Dis Sci* 1991; 36: 616–20.

197. Stacher G, Bergmann H, Wiesnagrotzki S, et al. Intraesophageal cisapride accelerates delayed gastric emptying and increases antral contraction amplitude in patients with primary anorexia nervosa. *Gastroenterology* 1987; 92: 1000–6.

198. Heyland DK, Tougas G, Cook DJ, Guyatt GH. Cisapride improves gastric emptying in mechanically ventilated, critically ill patients. A randomized, double-blind trial. *Am J Respir Crit Care Med* 1996; 154: 1678–83.

199. Madder GJ, Jamieson GG, Myers JC, Collins PJ. Effect of cisapride on delayed gastric emptying in gastrooesophageal reflux disease. *Gut* 1991; 32: 470–4.

200. Di Lorenzo C, Reddy SN, Villanueva-Meyer J, Mena I, Martin S, Hyman PE. Cisapride in children with chronic intestinal pseudoobstruction. An acute, double-blind, crossover, placebo-controlled trial. *Gastroenterology* 1991; 101: 1564–70.

201. Stacher G, Scherthaner G, Francesconi M, et al. Cisapride versus placebo for 8 weeks on glycemic control and gastric emptying in insulin-dependent diabetes: a double blind cross-over trial. *J Clin Endocrinol Metab* 1999; 84: 2357–62.

202. McClure RJ, Kristensen JH, Grauwaag A. Randomised controlled trial of cisapride in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1999; 80: F174–7.

203. Wei W, Ge ZZ, Lu H, Gao YJ, Hu YB, Xiao SD. Effect of mosapride on gastrointestinal transit time and diagnostic yield of capsule endoscopy. *J Gastroenterol Hepatol* 2007; 22: 1605–8.

204. Kanaizumi T, Nakano H, Matsui Y, et al. Prokinetic effect of AS-4370 on gastric emptying in healthy adults. *Eur J Clin Pharmacol* 1991; 41: 335–7.

205. Yamada M, Hongo M, Okuno Y, et al. Effect of AS-4370 on gastric motility in patients with diabetic autonomic neuropathy. *J Smooth Muscle Res* 1992; 28: 153–8.

206. Asai H, Udaka F, Hirano M, et al. Increased gastric motility during 5-HT4 agonist therapy reduces response fluctuations in Parkinson’s disease. *Parkinsonism Relat Disord* 2005; 11: 499–502.

207. Manini ML, Camilleri M, Goldberg M, et al. Effects of Velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation. *Neuрогastroenterol Motil* 2010; 22: 42–9.

208. Tack J, Broockaert D, Coulie B, Janssens J. The influence of cisapride on gastric tone and the perception of gastric distension. *Aliment Pharmacol Ther* 1998; 12: 761–6.

209. Manes G, Dominguez-Munoz JE, Leodolter A, Malfertheiner P. Effect of cisapride on gastric sensitivity to distension, gastric compliance and duodenogastric reflexes in healthy humans. *Dig Liver Dis* 2001; 33: 407–13.

210. Thumshirn M, Fruehauf H, Stutz B, Tougas G, Salter J, Fried M. Clinical trial: effects of tegaserod on gastric motor and sensory function in patients with functional dyspepsia. *Aliment Pharmacol Ther* 2007; 26: 1399–407.

211. Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology* 2001; 120: 354–60.

212. Elorza JM, Capdevila C. Double-blind parallel comparison of the gastrokinetic effects of clopobepide, domperidone and placebo in human volunteers with gastric stasis induced by glucagon. *Curr Ther Res* 1982; 31: S58–60.

213. Verhagen MA, Rooelofs JM, Edelbroek MA, Smout AJ, Akkersmans LM. The effect of cisapride on duodenal acid exposure in the proximal duodenum in healthy subjects. *Aliment Pharmacol Ther* 1999; 13: 621–30.

214. Rezende-Filho J, Di Lorenzo C, Dooley CP, Valenzuela JE. Cisapride stimulates antral motility and decreases biliary reflux in patients with severe dyspepsia. *Dig Dis Sci* 1989; 34: 1057–62.

215. Testoni PA, Ragnolo F, Fantl L, Passaretti S, Tittobello A. Longterm oral cisapride improves interdigestive antral motility in dyspeptic patients. *Gut* 1990; 31: 286–90.

216. Vaezi MF, Sears R, Richter JE. Placebo-controlled trial of cisapride in postgastrectomy patients with duodenogastroesophageal reflux. *Dig Dis Sci* 1996; 41: 754–63.

217. Marzio L, DiGiammarco AM, Capone F, et al. Effect of cisapride on human fasting gallbladder volume: a real-time ultrasonographic study. *Eur J Clin Pharmacol* 1986; 30: 631–3.

218. Takao M, Kubota Y, Fujimura K, et al. Effect of single and multiple administrations of cisapride on postprandial gallbladder emptying in healthy humans. *Intern Med* 1994; 33: 381–6.

219. Coremans G, Janssens J, Vantrappen G, Chaussade S, Ceccatelli P. Cisapride stimulates propulsive motility patterns in human jejunum. *Dig Dis Sci* 1988; 33: 1512–9.

220. Evans PR, Bak YT, Kellow JE. Effects of oral cisapride on small bowel motility in irritable bowel syndrome. *Aliment Pharmacol Ther* 1997; 11: 837–44.

221. Stacher G, Gaumann G, Mittelbach G, Schneider C, Steinringer H, Langer B. Effects of oral cisapride on interdigestive jejunal motor activity, psychomotor function, and side-effect profile in healthy man. *Dig Dis Sci* 1987; 32: 1223–30.

222. Stacher G, Steinringer H, Schneider C, Winklehner S, Mittelbach G, Gaumann G. Effects of cisapride on jejunal motor activity in fasting healthy humans. *Gastroenterology* 1986; 90: 1210–6.

223. Noor N, Small PK, Loudon MA, Hau C, Campbell FC. Effects of cisapride on symptoms and postcibal small-bowel motor function in patients with irritable bowel syndrome. *Scand J Gastroenterol* 1998; 33: 605–11.

224. Camilleri M, Brown ML, Malagelada JR. Impaired transit of chyme in patients with chronic constipation. A randomized, double-blind, placebo-controlled trial: effects of tegaserod on gastric motor and sensory function in patients with functional dyspepsia. *Aliment Pharmacol Ther* 2007; 26: 1399–407.
225. Krevsky B, Malmud LS, Maurer AH, Somers MB, Siegel JA, Fisher RS. The effect of oral cisapride on colonic transit. *Aliment Pharmacol Ther* 1987; 1: 293–304.

226. Bak YT, Kim JH, Lee CH. Cisapride in chronic idiopathic constipation: clinical response and effect on colonic transit time. *Korean J Intern Med* 1996; 11: 151–6.

227. Krevsky B, Maurer AH, Malmud LS, Fisher RS. Cisapride accelerates colonic transit in constipated patients with colonic inertia. *Am J Gastroenterol* 1989; 84: 882–7.

228. Jost WH, Schimrigk K. The effect of cisapride on delayed colonic transit time in patients with idiopathic Parkinson’s disease. *Wien Klin Wochenschr* 1994; 106: 673–6.

229. Geders JM, Gaing A, Bauman WA, Korsten MA. The effect of cisapride on segmental colonic transit time in patients with spinal cord injury. *Am J Gastroenterol* 1995; 90: 285–9.

230. Roberts JP, Benson MJ, Rogers J, Deeks JJ, Wingate DL, Williams NS. Effect of cisapride on distal colonic motility in the early postoperative period following left colonic anastomosis. *Dis Colon Rectum* 1995; 38: 139–45.

231. Poen AC, Felt-Bersma RJ, Van Dongen PA, Meuwissen SG. Effect of prucalopride, a new enterokinetic agent, on gastrointestinal transit and anorectal function in healthy volunteers. *Aliment Pharmacol Ther* 1999; 13: 1493–7.

232. Sloots CE, Poen AC, Kerstens R, et al. Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation. *Aliment Pharmacol Ther* 2002; 16: 759–67.

233. Coffin B, Farmachidi JP, Rueegg P, Bastie A, Bouhassira D. Tegaserod, a 5-HT4 receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects. *Aliment Pharmacol Ther* 2003; 17: 577–85.