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Mosapride
In Gastrointestinal Disorders

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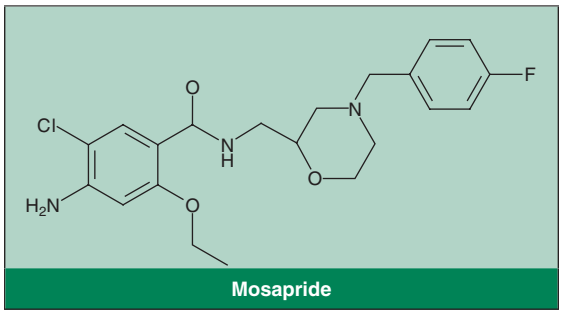
Contents

Abstract

- Mosapride was effective in improving overall symptoms in patients with gastrointestinal disorders, including chronic gastritis, gastro-oesophageal reflux disease and functional dyspepsia.
- Mosapride was more effective than teprenone in improving gastric stasis symptoms and gastric pain after 2 weeks of therapy ($p < 0.001$) in an open-label trial in 1042 patients with functional dyspepsia.
- Mosapride was as effective as famotidine and itopride, but more effective than tandospirone, in improving overall or individual symptoms of functional dyspepsia in randomized trials. However, in one randomized, double-blind trial in patients with mild to severe disease, the improvement in overall symptoms of functional dyspepsia did not differ significantly between mosapride or placebo treatment.
- Mosapride was well tolerated, with diarrhoea/loose stools, dry mouth, malaise and headache being reported in <5% of patients.

Features and properties of mosapride (Gasmotin®)	
Indication	
Gastrointestinal symptoms associated with chronic gastritis (Japan)	
Mechanism of action	
Prokinetic agent	
Dosage and administration	
Dose	5 mg
Frequency	Three times daily
Route of administration	Oral
Pharmacokinetic profile (single dose of 5 mg in volunteers; mean values)	
Maximum plasma concentration (C_{max})	30.7 ng/mL
Area under the concentration-time curve from time zero to infinity	67 ng • h/mL
Time to C_{max}	≈1 h
Elimination half-life	2 h
Adverse events (most common; 0.5–5%)	
Diarrhoea/loose stools, dry mouth, malaise and headache	



Mosapride

Commonly reported gastrointestinal disorders, including gastro-oesophageal reflux disease (GORD), functional dyspepsia and irritable bowel syndrome, have overlapping symptomatology.[1] Various committees and consensus groups have attempted to define these disorders. The Rome II committee defined functional dyspepsia as the presence of abdominal pain or discomfort centered in the epigastrium, which cannot be explained by upper gastrointestinal investigation and is present for at least 12 weeks over the last 12 months.[2] The more recent Rome III definition requires symptoms to be present for the last 3 months, with symptom onset at least 6 months before diagnosis.[3] According to the Rome criteria,[2,3] patients presenting with predominant or frequent (more than once weekly) heartburn or acid regurgitation do not have functional dyspepsia and are considered to have GORD. Patients with irritable bowel syndrome (pain or discomfort related to bowel pattern) are also not considered to have functional dyspepsia.[2,3]

Several factors have been identified as possible contributors to the pathogenesis of functional gastrointestinal disorders, including gastric acid secretion, abnormal gastroduodenal motility, visceral hypersensitivity, *Helicobacter pylori* infection, and the effects of stress and psychological factors.[1]

Pharmacological therapies for patients with gastrointestinal disorders include acid suppression with either histamine 2 receptor antagonists or proton pump inhibitors, regimens that eradicate *H. pylori*, antidepressants, and prokinetic agents.[1]

Prokinetic agents, including mosapride (Gasmotin®)[1] and cisapride, stimulate digestive motility. Both agents are thought to stimulate serotonin 5-HT_4 receptors in the gastrointestinal plexus, consequently increasing the release of acetylcholine and hence enhancing gastrointestinal motility and gastric emptying.[4] However, cisapride, which acts on serotonin receptors 5-HT_1 to 5-HT_4, has been associated with potentially fatal heart rhythm abnormalities and this agent has been withdrawn from several markets including the US.[1] Cisapride is a potent blocker of human ether-a-go-go-related gene (HERG) K^+ channels that are responsible for the repolarization phase of cardiac action potentials. Mosapride, which has little effect on K^+ channels,[5-7] is an alternative prokinetic agent that can be safely used in patients with upper gastrointestinal disorders.

This profile outlines the pharmacological properties and the clinical efficacy and tolerability of mosapride in patients with gastrointestinal disorders, including those diagnosed with chronic gastritis, functional dyspepsia or GORD.

1. Pharmacodynamic Profile

Mechanism of Action

- Mosapride is a selective 5-HT_4 receptor agonist with no affinity for 5-HT_1, 5-HT_2, adrenaline$_{\alpha 1}$, adrenaline$_{\alpha 2}$ or dopamine D_2 receptors.[8,9] The principal metabolite of mosapride (M1) is a weak serotonin 5-HT_3 antagonist.[10-12]

Effects on Gastrointestinal Motility

- Mosapride improved oesophageal motility, according to studies in volunteers[13,14] and in patients with GORD.[14,15] In a randomized, double-blind, crossover study in 41 patients with GORD,[15] pretreatment with mosapride 30 mg three times daily for 7 days resulted in significant increases in the amplitude of peristaltic contractions. The median amplitude of the contraction (assessed 10 cm above

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

the lower oesophageal sphincter) was 32.0 mmHg at baseline versus 34.0 mmHg during treatment with mosapride ($p < 0.05$). Mosapride had a significant ($p < 0.05$) effect on the peristaltic contraction duration compared with baseline, but no effect on the total number of oesophageal contractions.[15]

- Mosapride increased oesophageal bolus transit in 20 healthy volunteers in a randomized crossover study.[16] The proportion of liquid boluses completing transit (assessed using combined intraluminal impedance manometry) was higher with pretreatment with mosapride 30 mg/day for 3 days (92.2%) than with placebo (84.6%; $p < 0.01$).[16] The liquid bolus transit time was 6.3 seconds with mosapride and 6.4 seconds with placebo ($p = 0.06$), and was significantly shorter in patients with manometrically ineffective (contraction amplitude <30 mmHg) liquid swallows (8.9 vs >12.5 seconds; $p < 0.01$). However, there were no between-group differences in the amplitude and duration of oesophageal contractions.

- Mosapride shortened gastric emptying time, according to studies conducted in volunteers,[17] patients with gastrointestinal disorders,[18,19] patients with Parkinson's disease[20] and patients with diabetes mellitus.[21,22] For example, mean gastric emptying time (assessed by a double sampling test method in eight patients with chronic gastritis) was shortened by 19.4% after treatment with a single dose of mosapride 5 mg (from 133.4 to 107.6 minutes).[18] Similarly, in five patients with Parkinson's disease, mosapride 45 mg/day significantly reduced gastric emptying half-time from 155.4 to 61.7 minutes during treatment ($p = 0.038$).[20] Mosapride 10 mg administered 1 hour prior to capsular endoscopy reduced the gastric emptying time compared with that in the control group (13.5 vs 34.0 minutes; $p < 0.035$) in a randomized open-label study in 60 patients with various gastrointestinal disorders.[19]

- Mosapride augmented lower gastrointestinal motility in animal models[23] and in patients with lower gastrointestinal disorders.[24] Mosapride 15 mg/day for 3 months significantly shortened the total colonic transit time (110.8 hours at baseline vs 73.1 hours at treatment end; $p < 0.05$) and caudal (left) transit time (37.9 vs 25.2 hours; $p < 0.01$) in 14 patients with Parkinson's disease with constipation in an open-label study.[24]

- Mosapride enhanced defecation responses in animal models[25,26] and facilitated defecation in patients with lower gastrointestinal disorders.[24] Mosapride augmented the amplitude of rectal contractions during defecation (0.0–2.5 cmH_20; $p < 0.05$) in patients with Parkinson's disease.[24]

Effects on Acid Reflux Variables

- Mosapride reduced acid reflux variables (assessed using ambulatory pH monitoring) in patients with GORD (abnormal 24-hour pH recording of <4 for more than 5% of the time) in randomized, double-blind, crossover studies.[15,27]

- Pretreatment of 21 patients with GORD with mosapride 40 mg four times daily for 2 days was significantly more effective than placebo at reducing the median total number of reflux episodes (54 vs 61; $p < 0.05$), the median total number of reflux episodes >5 minutes (3 vs 5; $p < 0.05$), the mean total duration of the day with an intra-oesophageal pH <4 (6.9% vs 11%; $p < 0.01$) and the mean total oesophageal clearance (1.5 vs 2.0 min/reflux episode; $p < 0.05$).[27] Oesophageal acid reflux clearance was defined as the total time with pH <4 divided by the number of reflux episodes.

- In another study in 23 patients with GORD, pretreatment with mosapride 30 mg three times daily for 7 days, compared with baseline, significantly reduced the median proportion of time the pH was <4 while in the supine position (2.4% vs 9.7%; $p < 0.05$), the median total duration of the longest reflux episode (21.1 vs 41.9 min; $p < 0.05$) and the median total oesophageal clearance (1.5 vs 1.8 min/reflux episode; $p < 0.05$).[15]

Effects on Hormones

- Plasma levels of motilin increased after mosapride administration.[28,29] Following a single oral dose of mosapride 15 mg to five healthy volunteers,[28] peak plasma motilin levels (18.6 pg/mL)

were achieved after 60 minutes ($p < 0.01$ vs placebo), with levels returning to baseline levels by 180 minutes. The time when the increase in motilin occurred corresponded approximately with the time to peak plasma concentration of mosapride. Researchers suggested that the increased motilin may indicate an enhanced motor activity in the small intestine. Peak plasma gastrin levels (42.4 pg/mL) were also reached 60 minutes after administration of mosapride ($p < 0.01$ vs placebo). There was no significant change in plasma somatostatin or secretin levels.[28]

- Mosapride had no effect on plasma levels of prolactin, luteinizing hormone, follicle-stimulating hormone, estradiol or testosterone.[29]

Effects on K+ Channels and Cardiac Parameters

- Mosapride had little effect on the rapid component of delayed rectifying K^+ channels in isolated rabbit cardiomyocytes[5] or HERG-transfected cells (assessed using a whole cell patch clamp technique).[6,7] The K^+ current in HERG-transfected HEK293 cells was inhibited by cisapride, with a concentration that achieved half maximal inhibition of 9.4×10^{-9} mol/L, but not to any great extent with mosapride (4.8×10^{-6} mol/L).[6]
- In a rabbit model of the acquired long QT syndrome, mosapride, unlike cisapride, did not significantly lengthen the QTU interval.[5] Mosapride did not prolong the duration of the action potential of isolated rabbit Purkinje fibers[5] or guinea pig isolated papillary muscle.[30]
- Mosapride had no effect on cardiac parameters in ten healthy volunteers administered mosapride 15 mg/day.[31] After 7 days of mosapride therapy, there was no significant change from baseline in the RR or QT interval or corrected QT values. Moreover, while concomitant administration of erythromycin had an effect on the pharmacokinetics of mosapride (section 2), the coadministration of these drugs had no effect on cardiac parameters.
- Similarly, mosapride had no significant effect on the RR or QT interval, or corrected QT in 18 evaluable psychiatric patients who were also receiving various psychiatric drugs.[32]

2. Pharmacokinetic Profile

The pharmacokinetics of mosapride have been investigated in 9,[33] 10[31] and 35[34] healthy male volunteers, and in 6 young and 6 elderly healthy volunteers.[35]

- After oral administration of single doses of mosapride 5–40 mg, peak mosapride concentrations (C_{max}) were reached after ≈1 hour.[34] Both the C_{max} and area under the concentration-time curve from time zero to infinity (AUC_∞) increased in a dose-proportional manner. Mosapride mean C_{max} values after a single dose of mosapride 5, 10, 20 or 40 mg were 30.7, 63.6, 182.2 or 312.3 ng/mL. Respective mean AUC_∞ values were 67, 170, 380 and 699 ng • h/mL. Mean elimination half-lives ($t_{1/2}$) were 1.4–2.0 hours.
- Plasma C_{max} (52.0 ng/mL) of the active M1 metabolite occurred 0.5 hours after a single dose of mosapride 40 mg. Elimination of M1 ($t_{1/2}$ 4.3 hours) was slower than that of the parent drug.[34]
- There were no significant differences in the pharmacokinetic profiles of mosapride administered as single or multiple doses.[34] Plasma levels of the drug reached a steady state on day 2 after repeat administration of mosapride 10 or 20 mg three times daily.[34]
- The time to maximum concentration (t_{max}) of a single dose of mosapride 10 mg in the fasted state (0.6 hours) was significantly delayed in the presence of food (0.9 hours; $p < 0.05$); however, this delay was not considered to be of therapeutic importance.[34] Food had no significant effect on any other pharmacokinetic parameters.
- Mosapride is excreted in the urine and faeces. In the 48 hours after administration of a single dose of mosapride 5 mg, 0.1% of the total administered dose was excreted in the urine as the parent drug and 7.0% was excreted in the urine as the active metabolite.[34]
- The apparent total body clearance of mosapride is estimated to be 56.2–80.00 L/h and the apparent volume of distribution was 1.7–3.5 L/kg.[34]

- The protein binding rate in human plasma was 97% after a single dose of mosapride 20 or 40 mg.[34]
- Mosapride is primarily metabolized in the liver by cytochrome P450 3A4 to the active metabolite, a des-4-fluorobenzyl compound.[36]
- The pharmacokinetic profile of a single dose of mosapride 7.5 mg in elderly volunteers (aged 65–72 years) was generally similar to that in younger volunteers (aged 20–27 years).[35]
- Concomitant administration of mosapride 15 mg/day with erythromycin 1200 mg/day in volunteers increased the mosapride C_{max} from 42.1 ng/mL when administered alone to 65.7 ng/mL when coadministered with erythromycin.[31] The mosapride $t_{1/2}$ was prolonged from 1.6 to 2.4 hours, and the mosapride AUC from time zero to 4 hours (AUC_4) increased from 62 to 114 ng • h/mL. However, the coadministration of these drugs had no effect on cardiac parameters (see section 1).
- Administration of mosapride 5 mg to volunteers treated with omeprazole 20 mg/day significantly (all $p < 0.05$) increased the omeprazole C_{max} from 363.5 to 527.4 ng/mL and the omeprazole AUC_4 from 632 to 1041.3 ng • h/mL, and decreased the omeprazole t_{max} from 2.22 to 1.66 hours ($p < 0.05$).[33]

3. Therapeutic Efficacy

The terminology used to describe the symptoms of patients with gastrointestinal disorders has varied depending on the time and place the trial was conducted. The initial trials of mosapride (conducted in Japan) investigated the efficacy of this agent in improving upper gastrointestinal symptoms in patients described as having chronic gastritis/dyspepsia.[18,29,37-43] This section also reviews the more recently conducted randomized trials in patients presenting with similar symptoms, but who fulfilled the more recently proposed Rome II criteria[2] for functional dyspepsia.[44-49] Trials involving mosapride and employing the Rome III criteria to diagnose patients with functional dyspepsia have not yet been conducted.

Initial and more recently conducted trials have also investigated the efficacy of mosapride in patients with GORD.[15,27,43,50,51]

Clinical trials that investigated the efficacy of mosapride in postoperative patients with upper gastrointestinal disorders[52-54] and lower gastrointestinal disorders[55] will also be briefly reviewed.

Chronic Gastritis

This section reviews data from two large (n >200), 2-week, randomized, double-blind trials that investigated the efficacy of mosapride in patients with upper gastrointestinal symptoms described as having chronic gastritis.[40,41] In one of these studies, 253 evaluable patients with chronic gastritis were treated with mosapride 1.5–15 mg/day.[40] In the other study, 223 evaluable patients with chronic gastritis were treated with mosapride 5 mg three times daily or cisapride 2.5 mg three times daily.[41] Patients were examined by endoscopy or x-ray at baseline.[40,41]

- Mosapride was effective in improving overall symptoms (primary endpoint) in patients with chronic gastritis.[40,41] Mosapride (1.5–15 mg/day) was associated with a dose-related improvement in overall symptoms, with the cumulative percentage of patients being described as 'improved' and 'markedly improved' ranging from 48–78% in one study.[40] In the other study,[41] the final overall improvement rate was not significantly different between recipients of mosapride or cisapride, with the cumulative percentage of patients described as being 'improved' and 'markedly improved' being 75% in both groups (see figure 1).
- Mosapride was effective in improving feelings of epigastric fullness and epigastric pressure in these two large studies.[40,41] In the trial that compared the efficacy of mosapride with that of cisapride, the cumulative percentage of patients with 'improved' and 'much improved' epigastric fullness (72% vs 75%) or epigastric pressure (71% vs 71%) was not significantly different between the treatment groups.[41]

Functional Dyspepsia

The efficacy of mosapride has been investigated in patients with functional dyspepsia in randomized trials.[44-49] Patients had upper abdominal symptoms

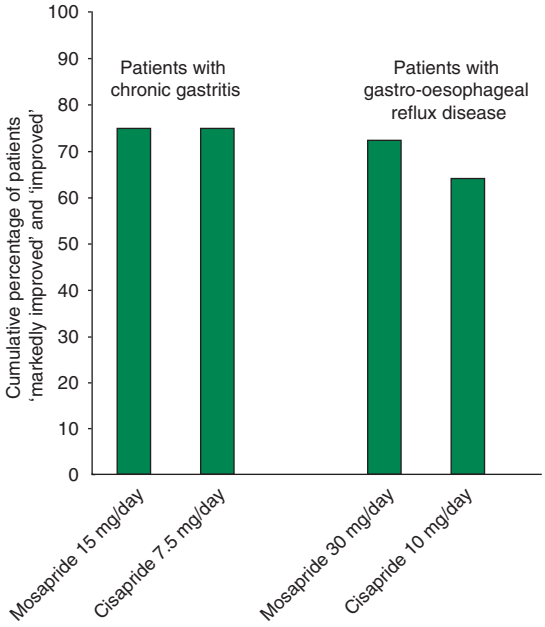


Fig. 1. Cumulative percentage of patients described as improved and markedly improved. In two randomized double-blind trials, patients with chronic gastritis (n = 223)[41] or gastro-oesophageal reflux disease (n = 120)[50] were treated for 2 weeks with mosapride 15[41] or 30[50] mg/day or cisapride 7.5[41] or 10[50] mg/day. The disease-specific improvements were evaluated by physicians on a 5-point scale; markedly improved, improved, somewhat improved, no change or worse.

in accordance with the Rome II criteria persisting for >4 days in the previous 2 weeks,[44] or >4[47] or >12[45,46,48,49] weeks. Organic disease (e.g. peptic ulcer, oesophagitis or gallstones) was excluded by endoscopy[44-49] and/or abdominal ultrasound.[45-48] Patients with GORD or those with irritable bowel syndrome were excluded from the trials.[44-46,48,49] Where stated, primary endpoints included the improvement in overall symptom severity score after 4[47] or 6[45] weeks of therapy, or the patient's or physician's global evaluation of efficacy after 2 weeks of therapy.[49]

Placebo Comparison

- The overall dyspeptic symptom score (primary endpoint) improved from baseline by 0.94, 0.88 and 0.89 after 6 weeks' treatment with mosapride 5 mg twice daily, 10 mg twice daily or 7.5 mg three times daily in a randomized, double-blind, multicentre, placebo-controlled trial in 566 evaluable patients with mild to severe functional dyspepsia.[45] However, the improvement in mosapride recipients was not significantly different from that in placebo recipients (0.90). Patients assessed daily symptom severity on a seven-grade Likert scale (0 = no symptoms; 6 = very severe symptoms). The mean overall dyspeptic scores at baseline were 2.77, 2.73, 2.76 and 2.72, respectively.
- The proportion of patients who were improved after 6 weeks of treatment was 59–61% in recipients of mosapride and 60% in recipients of placebo, with no significant between-group difference.[45] It has been suggested that the placebo response was very high[56] and that 51–58% of patients had upper abdominal pain at baseline (indicative of ulcer-like functional dyspepsia). It has been suggested that the outcomes of this trial may have been different if dysmotility-type functional dyspepsia had been specifically selected for at baseline.[56]

Comparison with Teprenone

- Mosapride was more effective than teprenone in improving individual symptoms of dyspepsia, according to a large, randomized, open-label trial in 1042 Japanese patients with functional dyspepsia.[44] After exclusion of patients with organic disease, 618 patients with symptoms persisting after 1 week were randomized to mosapride 5 mg three times daily (n = 311) or teprenone 50 mg three times daily (n = 307).
- After 2 weeks, gastric stasis symptom scores and epigastric pain scores (assessed on a three-step Likert scale) improved from baseline to a significantly greater extend with mosapride than with teprenone (see figure 2).[44]
- Health-Related Quality of Life Short-Form 36 (v2 J acute form) subscales in bodily pain, general health, vitality and mental health improved to a significantly greater extent with mosapride than with teprenone ($p < 0.05$).[44]
- The proportion of patients who felt that symptoms 'improved well', 'improved' or 'somewhat improved' was 91% with mosapride and 52% with teprenone ($p < 0.001$).[44]

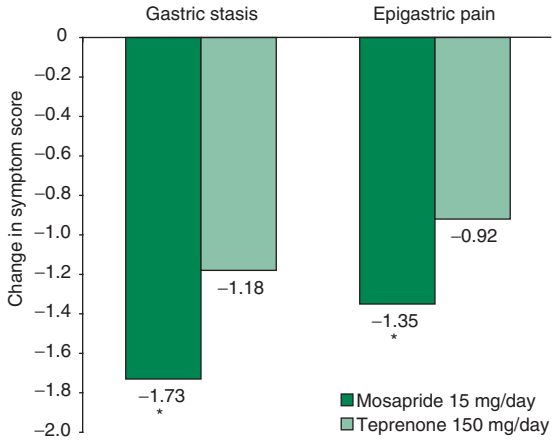


Fig. 2. Change in gastrointestinal symptom scores in patients with functional dyspepsia treated with mosapride or teprenone. Patients with endoscopically-proven functional dyspepsia (n = 618) were randomized to 2 weeks of treatment with mosapride 5 mg three times daily or teprenone 50 mg three times daily. Gastric stasis symptoms were defined as postprandial discomfort such as sensation of gastric stasis of food ingested, epigastric discomfort, epigastric heaviness or bloating. Epigastric pain was defined as pain in the upper abdomen. Symptom scores included assessments of severity and frequency (both on a three-step Likert scale). * $p < 0.001$ vs teprenone.[44]

Comparison with Famotidine or Tandospirone

Several randomized open-label studies have compared the efficacy of mosapride with that of famotidine or tandospirone in patients with functional dyspepsia (n = 81,[47] 79[46] or 62[48] evaluable patients). The severity of functional dyspepsia was assessed on a visual analogue scale (VAS). Patients were treated with mosapride 5 mg three times daily,[46-48] famotidine 10[47] or 20[46,48] mg twice daily, or tandospirone 10 mg three times daily[46,48] for 4[46,47] or 8[48] weeks.

- Mosapride was as effective as famotidine in improving overall symptoms of functional dyspepsia at study end in all three studies.[46-48]
- In the study in 81 patients,[47] 58.5% of mosapride recipients and 65.0% of famotidine recipients had more than a 3-point improvement in disease severity on a 10-point VAS (both $p < 0.05$ vs baseline) after 4 weeks of therapy.
- In a study in 62 evaluable patients,[48] the VAS scores (4 cm scale; 0 = excellent condition; 4 = worst condition) improved from 2.29 to 1.43 in mosapride recipients and from 2.04 to 0.83 in famotidine recipients after 8 weeks of treatment, with the improvement being significantly ($p < 0.01$) different from baseline after 2 weeks in both treatment groups. There was no significant improvement in VAS scores in tandospirone recipients.
- In the third study in 79 patients,[46] 9 of 25 mosapride recipients, 15 of 27 famotidine recipients and 4 of 27 tandospirone recipients had values <5 mm on a 100 mm VAS scale after 4 weeks, with the difference between the famotidine and tandospirone, but not famotidine and mosapride, groups being significant ($p < 0.002$).

Comparison with Itopride

- Global efficacy as judged by physicians (co-primary endpoint) was rated excellent in significantly ($p < 0.05$) more recipients of itopride 50 mg three times daily (80%) than mosapride 5 mg three times daily (50%) in a 2-week, randomized, double-blind study in 60 patients with functional dyspepsia.[49] Global efficacy as judged by patients (co-primary endpoint) was rated excellent in significantly ($p < 0.05$) more recipients of itopride (56.7%) than mosapride (30%). It should be noted that at baseline, the itopride group included more male patients (63% vs 37%; $p < 0.05$) and patients had a longer duration of dyspepsia (36 vs 22 months; $p < 0.05$) than in the mosapride group.
- Mosapride was not significantly different from itopride in improving individual symptoms of functional dyspepsia.[49] Epigastric pain, bloating, belching, heartburn, nausea, vomiting and anorexia significantly ($p < 0.05$) improved from baseline in both mosapride (37–100%) and itopride (51–100%) recipients.

Gastro-Oesophageal Reflux Disease

Data from short-term (<7 days), randomized, double-blind, crossover studies in patients with GORD[15,27] are reviewed in section 1. This section reviews data from larger (n = 120[50] or 61[51] patients), randomized, double-blind trials of longer duration (2[50] or 8[51] weeks).

Comparison with Cisapride

- Mosapride was as effective as cisapride in patients with GORD. In a phase III trial, there was no significant difference in the final global improvement (primary endpoint) between recipients of mosapride 30 mg/day or cisapride 10 mg/day.[50] The cumulative percentages of patients described as being markedly improved and improved was 72% in the mosapride group and 63% in the cisapride group (see figure 1).[50]
- The percentage of patients with an endoscopically proven cure was 44% in both treatment groups. The cumulative percentage of patients who were endoscopically proven to be cured and improved was 69% in the mosapride group and 61% in the cisapride group.[50]

Combination with Pantoprazole

- Combination therapy with pantoprazole and mosapride was more effective than pantoprazole alone in providing symptomatic relief to patients with erosive GORD.[51] Patients who reported heartburn and/or regurgitation at least two times per week for 6 weeks were randomized to combination therapy with pantoprazole 40 mg twice daily and mosapride 5 mg three times daily or monotherapy with pantoprazole 40 mg twice daily for 8 weeks.
- The number of patients who responded to therapy (symptom score ≤4 on a 19-point scale) was not statistically different between combination therapy or monotherapy with pantoprazole (89.2% vs 69.7%). However, at the end of 8 weeks, the mean symptom score was significantly lower in patients receiving combination therapy (1.67 vs 3.78; $p = 0.009$).[51]
- In patients with nonerosive GORD ($n = 29$), there was no significant difference in symptomatic response to either combination therapy or pantoprazole alone (77% vs 85%).[51] However, in patients with erosive GORD ($n = 32$), symptomatic responses occurred in more patients treated with combination therapy (94.7% vs 46.2%; $p = 0.003$). Endoscopically proven healing of oesophagitis was not significantly different between the two treatment groups (70.5% vs 54.5%).

Postoperative Gastrointestinal Disorder

- Mosapride was effective in improving symptoms of gastrointestinal disorders in postoperative ambulatory[52,53] or hospitalized[54] patients.
- Long-term administration of mosapride (5 mg three times daily for 12 weeks) improved epigastric digestive tract disorders in 29 postoperative ambulatory patients in an open-label trial.[53] The overall global improvement rating was 72.4%, with the improvement rates of subjective and objective symptoms such as anorexia, epigastric distention, nausea, vomiting and heartburn being ≈70%.[52]

Lower Gastrointestinal Disorders

- In non-comparative open-label studies, mosapride was effective in alleviating symptoms in patients with lower gastrointestinal disorders.[24,55] Mosapride alleviated abdominal pain and abdominal distention, loosened stools, shortened bowel transit and decreased flatus in the bowel in 11 patients with constipation-like irritable bowel syndrome.[24,55] Mosapride was also effective in reducing colonic transit time and augmenting the amplitude of rectal contractions in 14 patients with Parkinson's disease and constipation (see section 1).

4. Tolerability

Data on tolerability of mosapride in patients with gastrointestinal disorders have been obtained from the manufacturer's prescribing information,[36] phase III trials[41,50] and a postmarketing surveillance study in patients with non-ulcer dyspepsia.[57]

- Mosapride was well tolerated in clinical trials, with only minor adverse events such as diarrhoea/loose stools, dry mouth, malaise and headache being most commonly reported (<5% of patients).[36,41,50]
- According to physician-rated assessments in phase III trials, mosapride was considered to be safe in 96.6% of patients with GORD[50] and 97.5% of patients with chronic gastritis.[41]
- Adverse events occurred in 2.71% (23 of 848) of patients with dyspepsia who had received mosapride for more than 2 weeks, according to data from the post-marketing surveillance study. The most com-

mon adverse events were abdominal pain and loose stools (both 0.35%). No serious adverse events were reported.[57]

- Abnormal laboratory test values reported in clinical trials included eosinophilia (1.1% of patients), elevated triglycerides (1.0%), and elevated AST, ALT and gamma glutamyl transpeptidase levels (all 0.4%), according to data presented in the prescribing information.[36]
- There were no reports of QT interval prolongation associated with mosapride treatment, according to data from clinical trials in patients with gastrointestinal disorders (also see section 1).[41,50] However, there has been a single case report of *torsades de pointes* ventricular tachycardia in a patient with hypokalaemia who was receiving combination therapy with mosapride and flecainide.[58]

5. Dosage and Administration

The recommended usual dosage of mosapride for adults is 15 mg/day administered in three divided oral doses before or after meals.[36] If any improvement in gastrointestinal symptoms does not occur after approximately 2 weeks of therapy, then this agent should not be continued without supervision.[36]

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Mosapride: Current Status

Mosapride is currently approved for use in Japan in patients with gastrointestinal symptoms (heartburn, nausea/vomiting) associated with chronic gastritis.[36] This agent has been launched in China and South Korea,[59] and approval for its use in Thailand in patients with upper gastrointestinal symptoms associated with functional dyspepsia is currently being sought.[60] It is expected that submissions to market this drug in other Asian countries will also follow in the future.[61]

Mosapride was effective in improving overall symptoms and generally well tolerated in patients with a variety of gastrointestinal disorders, including chronic gastritis, gastro-oesophageal reflux disease and functional dyspepsia.

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