

# Sodium Picosulfate/Magnesium Citrate

## A Review of its Use as a Colorectal Cleanser

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**Data Selection**  
**Sources:** Medical literature published in any language since 1967 on ‘sodium picosulfate’, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.  
**Search strategy:** MEDLINE search terms were ‘sodium picosulfate’ or ‘sodium picosulphate’ or ‘DA-1773’; EMBASE and AdisBase search terms were ‘sodium picosulfate’ or ‘sodium picosulphate’. Searches were last updated 6 January 2009.  
**Selection:** Studies in patients undergoing endoscopy, surgery or x-ray examination and requiring colorectal cleansing. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.  
**Index terms:** Sodium picosulfate, sodium picosulphate, DA-1773, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

### Contents

Summary . . . . .	124
1. Introduction. . . . .	125
2. Pharmacological Properties . . . . .	126
2.1 Pharmacodynamic Profile . . . . .	126
2.2 Pharmacokinetic Profile. . . . .	127
3. Clinical Efficacy . . . . .	127
3.1 In Adults . . . . .	127
3.2 In Children and Adolescents. . . . .	129
4. Tolerability . . . . .	129
4.1 In Adults . . . . .	129
4.2 In Children and Adolescents. . . . .	132
5. Dosage and Administration . . . . .	132
6. Place of Sodium Picosulfate/Magnesium Citrate as a Colorectal Cleanser . . . . .	132

## Summary

### Abstract

Oral sodium picosulfate/magnesium citrate (CitraFleet<sup>®</sup>; Picolax<sup>®</sup>), consisting of sodium picosulfate (a stimulant laxative) and magnesium citrate (an osmotic laxative), is approved for use in adults (CitraFleet<sup>®</sup>; Picolax<sup>®</sup>) and/or adolescents and children (Picolax<sup>®</sup>) as a colorectal cleansing agent prior to any diagnostic procedure (e.g. colonoscopy or x-ray examination) requiring a clean bowel and/or surgery. It is dispensed in powder form (sodium picosulfate 0.01 g, magnesium oxide 3.5 g, citric acid 12.0 g per sachet), with the magnesium oxide and citric acid components forming magnesium citrate when the powder is dissolved in water.

In adult patients, two sachets of sodium picosulfate/magnesium citrate was at least as effective and well tolerated as oral magnesium citrate 17.7 or 35.4 g, or oral polyethylene glycol 236 g in adult patients undergoing a double-contrast barium enema procedure in three large, randomized, comparative clinical studies. In contrast, sodium picosulfate/magnesium citrate was less effective than a sodium phosphate enema preparation in two studies in patients undergoing flexible sigmoidoscopy. A similar number of patients receiving two sachets of sodium picosulfate/magnesium citrate or two 45 mL doses of oral sodium phosphate the day before a double-contrast barium enema procedure achieved satisfactory barium coating and none/minimal faecal residue in one study. However, the data from three of these studies should be interpreted with caution because the administrative regimens used differed from that recommended. Sodium picosulfate/magnesium citrate is also an effective and generally well tolerated colorectal cleansing agent in children and adolescents; the preparation was more effective than oral bisacodyl 0.01 or 0.02 g plus a sodium phosphate enema preparation in this population. Further research is thus required to accurately position sodium picosulfate/magnesium citrate and fully establish its efficacy and tolerability prior to various exploratory or surgical procedures. Nevertheless, oral sodium picosulfate/magnesium citrate provides a useful option in the preparation of the colon and rectum in adults, adolescents and children undergoing any diagnostic procedure (e.g. colonoscopy or x-ray examination) requiring a clean bowel and/or surgery.

### Pharmacological Properties

Oral sodium picosulfate/magnesium citrate acts locally in the colon as both a stimulant laxative, by increasing the frequency and the force of peristalsis (sodium picosulfate component), and an osmotic laxative, by retaining fluids in the colon (magnesium citrate component), to clear the colon and rectum of faecal contents. It is not absorbed in any detectable quantities. Sodium picosulfate is a prodrug: it is hydrolyzed by bacteria in the colon to the active metabolite 4,4'-dihydroxy-diphenyl-(2-pyridyl)methane.

Sodium picosulfate/magnesium citrate may be associated with a dehydrating effect, as evidenced by a reduction in bodyweight and increased haemoglobin levels; some at-risk patients may experience postural hypotension and older patients may require additional electrolytes.

### Clinical Efficacy

In three large (n > 100), randomized, single-blind clinical studies, two sachets of oral sodium picosulfate/magnesium citrate was at least as effective as oral magnesium citrate 17.7 or 35.4 g, or oral polyethylene glycol 236 g as a colorectal cleansing agent in adult patients undergoing a double-contrast barium enema procedure. In contrast, sodium picosulfate/magnesium citrate was less effective than a sodium phosphate enema preparation in two studies in patients undergoing flexible sigmoidoscopy. A similar number of patients receiving two sachets

of sodium picosulfate/magnesium citrate or two 45 mL doses of oral sodium phosphate the day before a double-contrast barium enema procedure achieved satisfactory barium coating and none/minimal faecal residue in one study. However, the data from three of these studies should be interpreted with caution because the administrative regimens used differed from that recommended.

In children and adolescents, sodium picosulfate/magnesium citrate was significantly more effective as a colorectal cleansing agent than oral bisacodyl 0.01 or 0.02 g plus a sodium phosphate enema preparation in a randomized, single-blind study; dosages were adjusted for age in this study.

## Tolerability

Oral sodium picosulfate/magnesium citrate is generally well tolerated in adult patients undergoing various investigational colorectal procedures. Adverse events were generally mild to moderate in intensity and mainly gastrointestinal in nature (e.g. abdominal cramps/pain, nausea); other common treatment-emergent adverse events included disturbance of daily activity, headache and sleep disturbance. This combination is at least as well tolerated as oral sodium phosphate or oral polyethylene glycol, with moderate/severe nausea and vomiting occurring less frequently in sodium picosulfate/magnesium citrate recipients than in those receiving oral sodium phosphate, and abdominal bloating/pain and nausea developing less often with sodium picosulfate/magnesium citrate than polyethylene glycol therapy.

The incidence of abdominal pain and sleep disturbance in sodium picosulfate/magnesium citrate versus oral magnesium citrate recipients was similar in one study, but significantly lower with sodium picosulfate/magnesium citrate in another. While the incidence of most adverse events was similar in recipients of sodium picosulfate/magnesium citrate and a sodium phosphate enema preparation, more patients receiving sodium picosulfate/magnesium citrate reported moderate/severe flatulence, incontinence and sleep disturbance, and more patients receiving the enema preparation reported rectal soreness. The tolerability profile of sodium picosulfate/magnesium citrate in patients aged >70 years is reportedly similar to that in patients aged <70 years.

Abdominal pain also occurred less frequently with sodium picosulfate/magnesium citrate than with oral bisacodyl plus a sodium phosphate enema preparation in children and adolescents.

## 1. Introduction

Optimal examination of the colon and rectum by colonoscopy and various radiological procedures (e.g. double-contrast barium enema procedure) and colorectal surgery requires a clean luminal environment for proper visualization.<sup>[1-3]</sup> Adequate preparation ensures ease of handling, a reduced bacterial load and, during surgery, the facilitation of palpation and a reduction in the risk of wound and peritoneal contamination.<sup>[4]</sup> In contrast, inadequate preparation of the colon and rectum can lead to cancelled procedures, increased procedural times, missed diagnoses and

an increased risk of peritoneal contamination.<sup>[2,5]</sup> The ideal colorectal cleansing agent is required to have a short ingestion and evacuation period, and to reliably empty the colon and rectum of all faecal material (formed and liquid), prevent gross or histological changes in the colonic mucosa, result in minimal patient discomfort (e.g. bloating, cramps, nausea) and produce no significant fluctuations in electrolytes or fluids.<sup>[1,3,5]</sup> The quality of a colorectal cleansing agent in preparing the colon and rectum directly affects the efficacy and safety of a procedure.<sup>[5]</sup> Thus, colorectal cleansing agents associated with excellent patient compliance are favoured by physicians intent

upon achieving a clean luminal environment for optimal diagnostic accuracy.<sup>[2,3,5]</sup>

Oral sodium picosulfate/magnesium citrate (CitraFleet<sup>®</sup>; Picolax<sup>®</sup>), consisting of sodium picosulfate and magnesium citrate, is used in adults (CitraFleet<sup>®</sup>,<sup>[6,7]</sup> Picolax<sup>®</sup>,<sup>8,9]</sup>) and/or adolescents and children (Picolax<sup>®</sup>)<sup>[8,9]</sup> to cleanse the colon and rectum prior to any diagnostic procedure (e.g. colonoscopy or x-ray examination) requiring a clean bowel and/or surgery. It is dispensed in powder form (sodium picosulfate 0.01 g, magnesium oxide 3.5 g, citric acid 12.0 g per sachet) with the magnesium oxide and citric acid components forming magnesium citrate when the powder is dissolved in water.<sup>[6-8]</sup> Discussion of sodium picosulfate/magnesium citrate formulations other than those mentioned previously are beyond the scope of this review. This review focuses on the efficacy and tolerability of sodium picosulfate/magnesium citrate as a colorectal cleansing agent in children, adolescents and adults undergoing colonoscopy, a double-contrast barium enema procedure or flexible sigmoidoscopy.

## 2. Pharmacological Properties

### 2.1 Pharmacodynamic Profile

Sodium picosulfate/magnesium citrate acts locally in the colon as both a stimulant laxative, by increasing the frequency and the force of peristalsis and promoting electrolyte and water retention in the colon (sodium picosulfate component), and an osmotic laxative, by retaining fluids in the colon (magnesium citrate component), to clear the colon and rectum of faecal contents.<sup>[6,8-10]</sup>

Oral sodium picosulfate/magnesium citrate has been associated with a dehydrating effect in studies of 10–41 adult patients requiring bowel preparation for various surgical procedures.<sup>[11-13]</sup> The 1.6–2.3 kg reduction in bodyweight<sup>[11-13]</sup> and 5% increase in haemoglobin levels<sup>[11]</sup> seen in patients after two sachets of sodium picosulfate/magnesium citrate 6–12 hours apart, 18–24 hours before bowel or renal surgery, indicate fluid loss associated with the combination despite un-

limited oral fluid intake. This loss of body fluid can result in postural hypotension in some at-risk patients.<sup>[11]</sup> A link between increased haemoglobin levels and the occurrence of headache in recipients of sodium picosulfate/magnesium citrate has also been noted.<sup>[14]</sup> The infusion of normal saline solution (1 L on two to three occasions) prior to surgery corrected the weight and blood pressure changes that occurred when patients received only oral fluids.<sup>[12,13]</sup> However, presurgical saline infusions did not correct the significant increase in pulse rate seen in sodium picosulfate/magnesium citrate recipients about to undergo colonic surgery in two studies (mean increases of 6–12% in supine patients;  $p < 0.05$ ).<sup>[11,12]</sup>

Serum chloride,<sup>[15]</sup> potassium,<sup>[12,16]</sup> sodium<sup>[15,16]</sup> and urea<sup>[16]</sup> levels were significantly ( $p < 0.05$  vs baseline) reduced in three studies involving 35–112 adult recipients of two sachets of sodium picosulfate/magnesium citrate, 4–6 hours apart, 18–48 hours before colon/bowel surgery or barium enema procedures.<sup>[12,15,16]</sup> The losses of chloride, potassium and sodium were greater in patients receiving the combination 48 versus 24 hours prior to surgery ( $p < 0.01$ ).<sup>[15]</sup> In one study, a statistically significant ( $p < 0.0001$  vs baseline) elevation in serum magnesium levels occurred following the administration of sodium picosulfate/magnesium citrate; no change was observed in glucose levels.<sup>[16]</sup> In contrast, no significant changes in plasma calcium, creatinine, potassium or sodium levels occurred in a single-centre study in which 61 patients aged 31–87 years received two sachets of oral sodium picosulfate/magnesium citrate prior to colonoscopy ( $n = 31$ ) or colorectal resection ( $n = 31$ ).<sup>[17]</sup> However, in the same study, statistically significant ( $p < 0.01$ ) reductions in plasma urea levels and statistically significant ( $p < 0.005$ ) elevations in plasma magnesium levels were observed following bowel preparation. These changes were not considered to be clinically significant in younger, more healthy patients; one study found that the reduction in serum potassium levels was significant only in patients aged  $> 60$  years.<sup>[16]</sup>

Bowel preparation (two sachets of sodium picosulfate/magnesium citrate, 4 hours apart) 24 or

48 hours before bowel surgery was rated by surgeons, using a 4-point scale, during the surgical procedure as satisfactory (no or minimal faecal residue) in 65% and 28% of recipients ( $n = 17$  and  $18$ ).<sup>[15]</sup> In the same study, potentially explosive colonic methane was found in 29% and 55% of recipients.<sup>[15]</sup>

## 2.2 Pharmacokinetic Profile

Sodium picosulfate/magnesium citrate is locally active in the colon and is not absorbed in any detectable quantities.<sup>[6-8]</sup> Sodium picosulfate is hydrolyzed by bacteria in the colon to the active metabolite 4,4'-dihydroxydiphenyl-(2-pyridyl)methane.<sup>[18]</sup>

## 3. Clinical Efficacy

The efficacy of oral sodium picosulfate/magnesium citrate as a colorectal cleansing agent prior to various exploratory procedures has been examined in several fully published, large ( $n > 100$ ), randomized, single-blind, comparative clinical studies in adult patients (section 3.1).<sup>[19-24]</sup> Studies in adult patients with fewer than 100 participants have not been included in this review. The efficacy of oral sodium picosulfate/magnesium citrate has been investigated to a more limited extent in one fully published study in children and adolescents (section 3.2).<sup>[25]</sup>

### 3.1 In Adults

Three large ( $n = 102$ – $1219$ ), randomized studies in adult patients (aged 20–83 years) investigating the comparative efficacy of one to two sachets of oral sodium picosulfate/magnesium citrate versus oral magnesium citrate in patients undergoing a double-contrast barium enema procedure or a sodium phosphate enema preparation in patients undergoing flexible sigmoidoscopy are summarized in table I.<sup>[19-21]</sup> Data from three randomized studies ( $n = 196$ ,<sup>[23]</sup>  $194$ <sup>[22]</sup> and  $150$ <sup>[24]</sup>) comparing the efficacy of oral sodium picosulfate/magnesium citrate with that of oral sodium phosphate,<sup>[22]</sup> oral magnesium citrate<sup>[23]</sup> or oral polyethylene glycol<sup>[24]</sup> in patients

undergoing double-contrast barium enema procedures are also discussed.

All studies were single-blind (i.e. radiologist or sigmoidoscopist blinded to treatment regimen).<sup>[19-24]</sup> Sodium picosulfate/magnesium citrate was dispensed in powder form and dissolved in 150 mL of water prior to administration.<sup>[6-9]</sup>

Patients were excluded if they had colorectal cancer,<sup>[19]</sup> inflammatory bowel disease,<sup>[19]</sup> type 1 diabetes mellitus,<sup>[23]</sup> had undergone colorectal endoscopy in the previous 2 years,<sup>[19]</sup> and/or were undergoing instant or single-contrast enema procedures.<sup>[23]</sup>

Diverse endpoints were used to assess efficacy, with the most common being subjective ratings of colorectal cleansing (see table I for definitions of the subjective ratings).<sup>[19-21]</sup>

A sodium phosphate enema preparation was significantly more effective as a colorectal cleanser than a single sachet of oral sodium picosulfate/magnesium citrate, in terms of 'excellent',<sup>[19,20]</sup> 'good',<sup>[19,20]</sup> or 'adequate',<sup>[20]</sup> colorectal cleansing, in two studies in patients undergoing flexible sigmoidoscopy (table I). 'Excellent' or 'good' colorectal cleansing was achieved in  $\approx 75\%$  of sodium phosphate enema preparation recipients, but was observed in a lower proportion of sodium picosulfate/magnesium citrate recipients (table I).<sup>[19,20]</sup> Similarly, an 'adequate' or better result was observed in more sodium phosphate enema preparation than sodium picosulfate/magnesium citrate recipients.<sup>[19,20]</sup> Mean mucosal visibility of the first 45 cm of the colon was 88–95% and 82–91% in sodium phosphate enema preparation and sodium picosulfate/magnesium citrate recipients in the study by Atkin et al.<sup>[19]</sup> Furthermore, flexible sigmoidoscopy was considered to be successfully performed in the study by Drew et al.<sup>[20]</sup> in significantly more sodium phosphate enema preparation than sodium picosulfate/magnesium citrate recipients (86% vs 65%;  $p < 0.05$ ).<sup>[20]</sup> In both of these studies, the dosage of sodium picosulfate/magnesium citrate may have been too low, since the recommended dosage is two sachets 6–8 hours apart on the day prior to the procedure (section 5).<sup>[6-8]</sup> However, the authors of one study indicated that a single sachet is

**Table I.** Comparative efficacy of oral sodium picosulfate/magnesium citrate (NaPS/MgC) as a colorectal cleansing agent. Summary of large ( $n > 100$ ), randomized, single-blind (i.e. radiologist or sigmoidoscopist blinded to treatment regimen), single-centre (unless stated otherwise) studies in adult patients (pts) requiring colorectal preparation for various exploratory procedures. Each NaPS/MgC sachet contained sodium picosulfate 0.01 g, magnesium oxide 3.5 g and citric acid 12.0 g; the contents were dissolved in water prior to consumption. Patient data were grouped to calculate colorectal cleansing percentages. Analyses were per-protocol<sup>[19]</sup> or intent-to-treat<sup>[20,21]</sup>

Study	Treatment	Dosage (time relative to procedure) and preparation	No. of pts	Colorectal cleansing <sup>a</sup> (% pts)	
				≥good	≥adequate/ satisfactory
<b>Vs an NaP enema preparation in pts undergoing flexible sigmoidoscopy</b>					
Atkin et al. <sup>[19]b</sup>	NaPS/MgC	1 sachet 18 h prior; FO thereafter	584	65	82
	NaP enema <sup>c</sup>	1 enema 1 h prior to leaving home; FO thereafter	635	76 <sup>d</sup>	86
Drew et al. <sup>[20]</sup>	NaPS/MgC	1 sachet night prior	46	52	74
	NaP enema <sup>c</sup>	1 enema 2 h prior	56	75	93 <sup>e</sup>
<b>Vs oral MgC in pts undergoing DCBE</b>					
Swarbrick et al. <sup>[21]b</sup>	NaPS/MgC	1 sachet before breakfast and 1 sachet pm day prior; 3-day LRD prior to DCBE, FO thereafter	102	75 <sup>f</sup>	95
	MgC <sup>e</sup>	1 sachet evening on day prior; 3-day LRD prior to DCBE, FO thereafter	104	40	81

a Assessed using a 3-item (good, satisfactory, unsatisfactory)<sup>[21]</sup> or 4-item (excellent, good, adequate, poor)<sup>[19,20]</sup> scale.

b Multicentre study.

c Fletchers' NaP enema preparation<sup>[19]</sup> (volume 128 mL) contained sodium acid phosphate 10% and sodium phosphate 8%; Fleet® NaP enema preparation<sup>[20]</sup> contained 19 g of monobasic sodium phosphate and 7 g of dibasic sodium phosphate per 118 mL.

d  $p < 0.001$  for trend in the distribution of patients across four colorectal cleansing quality groups vs NaPS/MgC.

e Each sachet contained magnesium citrate equivalent to magnesium oxide 5 g (magnesium carbonate 11.6 g and anhydrous citric acid 17.8 g, which on the addition of water forms MgC 17.7 g).

**DCBE** = double-contrast barium enema procedure; **FO** = fluids only; **LRD** = low-residue diet; **MgC** = magnesium citrate; **NaP enema** = sodium phosphate enema; **pm** = afternoon; \*  $p < 0.01$  vs NaPS/MgC; +  $p < 0.001$  vs MgC.

routinely used in their UK hospital for flexible sigmoidoscopy, while two sachets are used for colonoscopy.<sup>[19]</sup>

Similar numbers of patients receiving two sachets of oral sodium picosulfate/magnesium citrate ( $n = 83$ ) or two 45 mL doses of oral sodium phosphate (2.4 g monobasic and 0.9 g dibasic sodium phosphate per 5 mL) [ $n = 111$ ] the day before a double-contrast barium enema procedure achieved satisfactory barium coating (86% vs 89%) and none/minimal faecal residue (86% vs 80%) in one study.<sup>[22]</sup>

Colorectal cleansing was significantly more effective with two sachets of oral sodium picosulfate/magnesium citrate than with one sachet of oral magnesium citrate 17.7 g on the day prior to a double-contrast barium enema procedure after 3 days of low residue diet ( $p < 0.001$ ; table I).<sup>[21]</sup> Furthermore, faecal residue was absent in a significantly higher proportion of oral sodium picosulfate/magnesium citrate than oral magne-

sium citrate recipients (72% vs 38%;  $p < 0.001$ ).<sup>[21]</sup> However, the findings of this study are not unexpected, given that the recommended dose of magnesium citrate is two sachets 6–8 hours apart on the day prior to the procedure.<sup>[26]</sup> No significant difference in the amount of residual stool/water was seen between two sachets of sodium picosulfate/magnesium citrate ( $n = 58$ ) and two sachets of magnesium citrate 17.7 g ( $n = 63$ ) after 5 days of low-residue diet in a smaller study.<sup>[23]</sup> Barium coating was 'good' or 'satisfactory' in similar numbers of patients in both treatment groups in the former study (96% vs 93%).<sup>[21]</sup> with no significant difference observed between sodium picosulfate/magnesium citrate and magnesium citrate recipients in the latter study.<sup>[23]</sup> Both sodium picosulfate/magnesium citrate and magnesium citrate were more effective than sodium picosulfate/magnesium citrate plus a water enema preparation ( $n = 63$ ) in the latter study ( $p < 0.01$ ).<sup>[23]</sup>

No significant differences were found in the overall quality of the preparation (faecal clearance/polyp detection plus mucosal coating plus residual fluid) in 143 patients who received two sachets of oral sodium picosulfate/magnesium citrate 7 hours apart on the day before a double-contrast barium enema procedure ( $n=45$ ), two sachets of sodium picosulfate/magnesium citrate plus 3 days' low-residue diet ( $n=51$ ) or four packets of an oral preparation of polyethylene glycol plus 1 day of low-residue diet ( $n=47$ ).<sup>[24]</sup> Each polyethylene glycol packet contained polyethylene glycol 3350 59 g, sodium sulfate 5.7 g, sodium bicarbonate 1.7 g, sodium chloride 1.5 g, potassium chloride 0.7 g and aspartame. The contents of each packet were dissolved in 1 L of water and all four packets consumed over 4–6 hours.<sup>[24]</sup> Mean faecal clearance scores of  $\geq 2$  ('acceptable') were reported in 84%, 76% and 76% of patients in the respective treatment groups.<sup>[24]</sup> However, the two sodium picosulfate/magnesium citrate regimens were more effective than polyethylene glycol in the quality of barium coating (all colon segments) and the amount of residual fluid (all except the sigmoid colon/rectum); furthermore, faecal clearance in the descending colon (but not the other segments) in recipients of sodium picosulfate/magnesium citrate without the low-residue diet was more effective than that in the other two groups ( $p < 0.05$ ) [figure 1].<sup>[24]</sup>

### 3.2 In Children and Adolescents

The efficacy of oral sodium picosulfate/magnesium citrate as a colorectal cleansing agent in children and adolescents has been investigated in a single-blind, single-centre study.<sup>[25]</sup> Participants were children and adolescent outpatients (aged 18 months to 16 years) who were scheduled to undergo colonoscopy. Inpatients and those undergoing non-elective colonoscopy were excluded.<sup>[25]</sup> Patients were randomized to two doses of sodium picosulfate/magnesium citrate (each ranging from a quarter of a sachet to one sachet according to age) 24 and 18 hours prior to colonoscopy ( $n=32$ ) or oral bisacodyl 5 or 10 mg/day (according to age) for 2 days prior to colonos-

copy ( $n=31$ ).<sup>[25]</sup> Participants in the latter group also received 64 or 128 mL of an enema preparation containing sodium acid phosphate 10% and sodium phosphate 8% on the morning of the procedure. Colorectal cleansing was assessed as 'excellent' or 'good' in 100% of the sodium picosulfate/magnesium citrate and 71% of the oral bisacodyl plus a sodium phosphate enema preparation treatment groups ( $p < 0.01$ ).<sup>[25]</sup>

## 4. Tolerability

Oral sodium picosulfate/magnesium citrate was generally well tolerated in adults<sup>[19–24]</sup> and in paediatric and adolescent patients<sup>[25]</sup> participating in randomized, single-blind clinical studies (see section 3 for further design details).

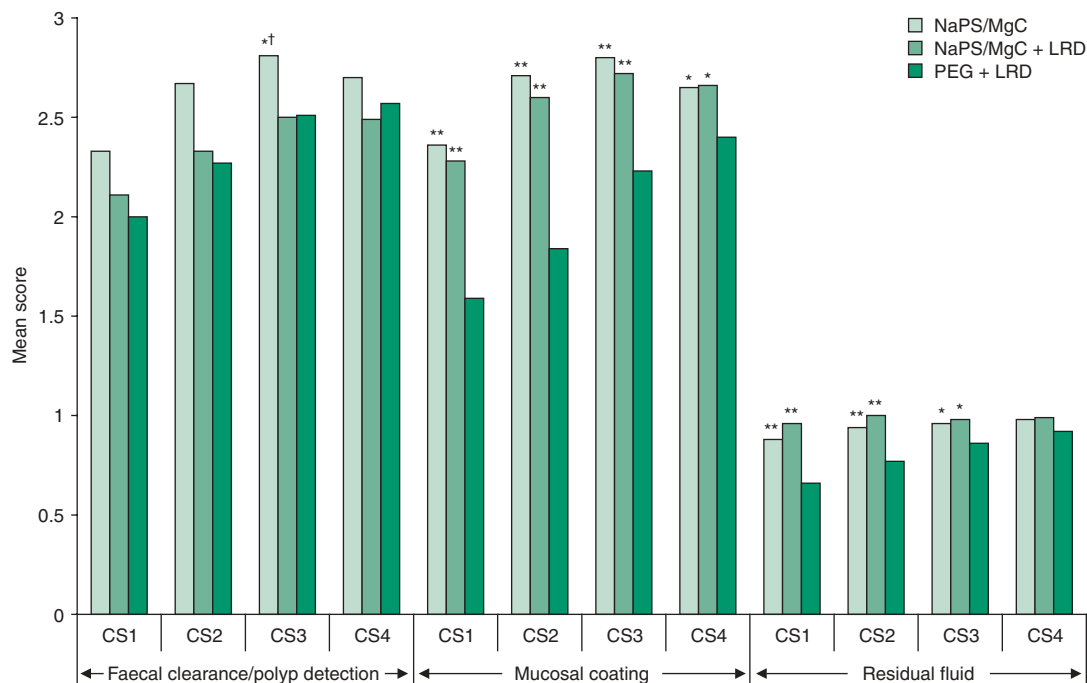
Additional tolerability data in this section are derived from a multicentre study,<sup>[27]</sup> an Australian Adverse Drug Reactions Bulletin<sup>[28]</sup> and a Canadian Association of Gastroenterology position paper.<sup>[29]</sup>

### 4.1 In Adults

Adverse events associated with oral sodium picosulfate/magnesium citrate were, where reported, generally gastrointestinal in nature<sup>[19–22,24]</sup> and generally mild to moderate in intensity.<sup>[22]</sup>

The most frequently reported treatment-emergent adverse event (all grades) in adult patients receiving sodium picosulfate/magnesium citrate was abdominal cramps/pain (0–45% of patients).<sup>[20–22,24]</sup> Where stated, other common treatment-emergent adverse events in sodium picosulfate/magnesium citrate recipients included sleep disturbance (54%<sup>[22]</sup> and 45%<sup>[21]</sup>), disturbance of daily activity (70%<sup>[22]</sup> and 43%<sup>[21]</sup>), headache (34%<sup>[22]</sup> and 9%<sup>[24]</sup>) and nausea (7–28%<sup>[20–22,24]</sup>).

The incidence of moderate/severe abdominal pain/cramps (9% vs 10%), nausea/vomiting (3% vs 2%) and faintness/dizziness (4% vs 3%) was generally similar in patients receiving oral sodium picosulfate/magnesium citrate or sodium phosphate enema preparation before flexible sigmoidoscopy.<sup>[19]</sup> However, 95% confidence intervals indicated significant differences favouring



**Fig. 1.** Comparative efficacy of oral sodium picosulfate/magnesium citrate (NaPS/MgC) as a colorectal cleanser in adult patients undergoing a double-contrast barium enema procedure. Faecal clearance/polyp detection, mucosal coating clarity and residual fluid scores for four segments of the colon: caecum to hepatic flexure (CS1); transverse colon to splenic flexure (CS2); descending colon (CS3); sigmoid colon and rectum (CS4). Patients received two sachets of NaPS/MgC 7 hours apart on the day prior to the procedure with ( $n=51$ ) or without ( $n=45$ ) a preliminary 3-day low-residue diet (LRD), or four packets of oral polyethylene glycol preparation (PEG) plus a 1-day LRD ( $n=47$ ) in a randomized, single-blind study.<sup>[24]</sup> Each NaPS/MgC sachet contained NaPS 0.01 g, magnesium oxide 3.5 g and citric acid 12.0 g. Each PEG packet contained PEG 3350 59 g, sodium sulfate 5.7 g, sodium bicarbonate 1.7 g, sodium chloride 1.5 g, potassium chloride 0.7 g and aspartame. The colonic segments were scored on a scale of 0 to 3 (higher score optimal). Data reported are for the per-protocol population. \*  $p < 0.05$ , \*\*  $p < 0.01$  vs PEG; †  $p < 0.05$  vs NaPS/MgC + LRD.

the enema preparation in the incidences of moderate/severe flatulence (10% vs 4%), incontinence (5% vs 1%) and sleep disturbance (13% vs 1%) [although there were no differences on the day after the procedure], and a significant difference favouring sodium picosulfate/magnesium citrate in the incidence of rectal soreness (9% vs 14%).<sup>[19]</sup>

Oral sodium picosulfate/magnesium citrate was at least as well tolerated as oral sodium phosphate in one clinical study, with moderate/severe nausea and vomiting occurring less often in sodium picosulfate/magnesium citrate recipients than in those receiving oral sodium phosphate ( $p < 0.001$ ) [figure 2].<sup>[22]</sup>

The nature of treatment-emergent adverse events was generally similar in oral sodium picosulfate/magnesium citrate and oral magne-

sium citrate recipients in two studies.<sup>[21,23]</sup> In one study, 31% and 32% of patients receiving sodium picosulfate/magnesium citrate (whether patients received sodium picosulfate/magnesium citrate alone or followed by a water enema was not specified) or magnesium citrate ( $n=63$ ) were asymptomatic (experienced no abdominal pain, sleep disturbance or a disturbance in normal daily activities).<sup>[23]</sup> However, in the other study, significantly fewer sodium picosulfate/magnesium citrate than magnesium citrate recipients experienced abdominal pain (18% vs 37%;  $p < 0.01$ ) and sleep disturbance (45% vs 67%;  $p < 0.01$ ), whereas the incidence of disturbance in daily activity was higher in patients receiving sodium picosulfate/magnesium citrate (43% vs 17%;  $p < 0.001$ ).<sup>[21]</sup>

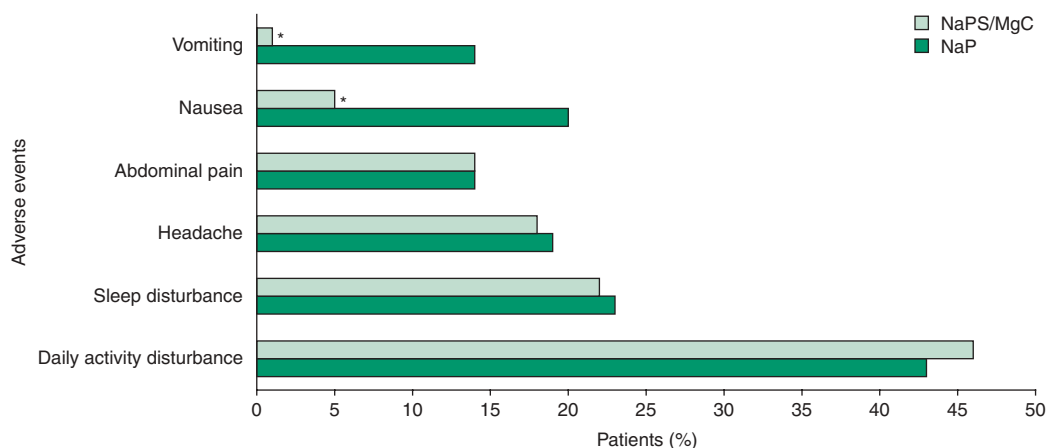
In patients undergoing a double-contrast barium enema procedure,<sup>[24]</sup> oral sodium picosulfate/magnesium citrate (with or without a low-residue diet) was at least as well tolerated as oral polyethylene glycol. Significantly more sodium picosulfate/magnesium citrate recipients with or without a low-residue diet versus polyethylene glycol recipients were asymptomatic (27% and 33% vs 6%; both  $p < 0.001$ ), with significantly less abdominal bloating (29% and 31% vs 77%; both  $p < 0.001$ ), abdominal pain (35% and 38% vs 64%; both  $p < 0.01$ ) and/or nausea (11% and 7% vs 64%; both  $p < 0.01$ ) experienced by recipients of sodium picosulfate/magnesium citrate with or without a low-residue diet versus polyethylene glycol.<sup>[24]</sup> The respective incidences of anal irritation (8%, 11% and 11%), headache (2%, 9% and 13%) and vomiting (2%, 0% and 4%) did not significantly differ between the treatment groups.<sup>[24]</sup>

The tolerability profile of oral sodium picosulfate/magnesium citrate in patients aged  $>70$  years was reportedly similar to that in patients aged  $<70$  years (no quantitative data reported).<sup>[24]</sup> This was supported by data from a multicentre study in 165 patients (aged 22–86 years) who received sodium picosulfate/magnesium citrate

( $n=83$ ) or polyethylene glycol ( $n=82$ ).<sup>[27]</sup> In this study, there was no significant correlation between age and the patients' overall rating of their subjective experience of the bowel preparation.<sup>[27]</sup>

Between 1997 and 2002, eight episodes of severe electrolyte disturbances (resulting in convulsions [5 episodes], syncope, [1] unconsciousness [1] and metabolic acidosis [1]) and four episodes of syncope and dehydration without documented electrolyte disturbances were reported by the Australian Adverse Drug Reactions Committee following the administration of oral sodium picosulfate/magnesium citrate.<sup>[28]</sup> Furthermore, between 1995 and 2001, 21 adverse events, including five episodes of serious electrolyte disturbances (but no deaths), were described by Ferring Pharmaceuticals UK.<sup>[29]</sup>

Where reported, acceptability of oral sodium picosulfate/magnesium citrate was better than polyethylene glycol,<sup>[24,27]</sup> worse than a sodium phosphate enema preparation<sup>[20]</sup> and better than oral sodium phosphate.<sup>[22]</sup> Sodium picosulfate/magnesium citrate and oral magnesium citrate were rated as 'pleasant to taste' by a similar proportion of adult patients in both treatment groups,<sup>[21]</sup> whereas patients preferred the taste of



**Fig. 2.** Tolerability of oral sodium picosulfate/magnesium citrate (NaPS/MgC) as a colorectal cleanser in adult patients undergoing a double-contrast barium enema procedure.<sup>[22]</sup> Moderate/severe treatment-emergent adverse events occurring in patients receiving NaPS/MgC ( $n=83$ ) or oral sodium phosphate (NaP) [ $n=111$ ] in a randomized, single-blind study. Patients received two sachets of NaPS/MgC or two doses of NaP, one in the morning and one in the afternoon, on the day prior to the double-contrast barium enema procedure.<sup>[22]</sup> Each NaPS/MgC sachet contained NaPS 0.01 g, magnesium oxide 3.5 g and citric acid 12.0 g. Each 5 mL of the oral NaP preparation contained sodium phosphate monobasic 2.4 g and sodium phosphate dibasic 0.9 g. Data reported are for the intent-to-treat population.<sup>[22]</sup> \*  $p < 0.001$  vs NaP.

sodium picosulfate/magnesium citrate to that of oral sodium phosphate.<sup>[22]</sup>

#### 4.2 In Children and Adolescents

Abdominal pain was significantly less frequent with oral sodium picosulfate/magnesium citrate than with oral bisacodyl plus a sodium phosphate enema preparation in children and adolescents (figure 3).<sup>[25]</sup> Moderate or severe distress (as a result of the lack of solid food) and minor distress (as a result of the enema preparation) were reported in six sodium picosulfate/magnesium citrate and six bisacodyl plus a sodium phosphate enema preparation recipients.<sup>[25]</sup> Patient compliance was reported as 'excellent' in both treatment groups.<sup>[25]</sup>

### 5. Dosage and Administration

Oral sodium picosulfate/magnesium citrate is indicated for use as a colorectal cleansing agent in adults (CitraFleet<sup>®</sup>;<sup>[6,7]</sup> PicoLax<sup>®</sup>) and/or adolescents and children (PicoLax<sup>®</sup>)<sup>[8]</sup> undergoing any diagnostic procedure (e.g. colonoscopy or x-ray examination) requiring a clean bowel<sup>[6-8]</sup>

and/or surgery<sup>[8]</sup> in the UK<sup>[6,8]</sup> and in several other European countries, including France, Germany, Ireland, Italy, Portugal and Spain, under the mutual recognition procedure with the UK as the reference state.<sup>[7]</sup> Two sachets of sodium picosulfate/magnesium citrate are recommended in those aged  $\geq 9$ <sup>[8]</sup> or  $\geq 18$ <sup>[6,7]</sup> years. Each sachet should be reconstituted in approximately 150 mL of water, with the first dose administered before 8am on the day prior to the procedure and the second dose 6–8 hours later.<sup>[6-9]</sup>

The recommended doses for children aged 1–2, 2–4 and 4–9 years is one-quarter of a sachet in both the morning and afternoon, half of a sachet in both the morning and afternoon, and one sachet in the morning and half of a sachet in the afternoon, respectively, on the day prior to the procedure.<sup>[8,9]</sup>

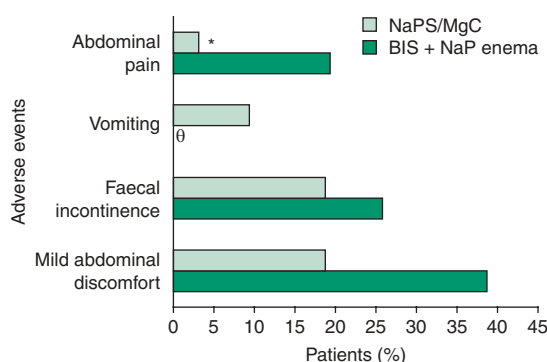
On the day prior to the procedure, a low-residue diet is recommended; patients are advised to consume approximately 250 mL of water or other clear fluids every hour to avoid dehydration.<sup>[6-8]</sup> It is advised that the period of bowel cleansing should not exceed 24 hours, as the risk of water and electrolyte imbalance may be increased with longer bowel preparation times (see section 2.1).<sup>[6-8]</sup>

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

### 6. Place of Sodium Picosulfate/Magnesium Citrate as a Colorectal Cleanser

The quality of a cleansing agent in preparing the colon and rectum directly affects the efficacy and safety of an investigational (e.g. colonoscopy) or surgical procedure.<sup>[5]</sup> Both an effective colorectal cleansing agent and good patient compliance are required in order to achieve a clean luminal environment and optimal diagnostic accuracy.<sup>[2,5]</sup>

Early colorectal cleansing agents consisted of dietary restrictions (e.g. 1–4 days of liquids or foods that produce minimal colonic faecal residue), enema preparations (e.g. tap water) and



**Fig. 3.** Tolerability profile of oral sodium picosulfate/magnesium citrate (NaPS/MgC) as a colorectal cleanser in children and adolescents undergoing a colonoscopy. Adverse events occurring in patients receiving two doses of NaPS/MgC (each ranging from a quarter of a sachet to one sachet according to age) 24 and 18 hours prior to colonoscopy (n=32) or oral bisacodyl (BIS) 5 or 10 mg/day (according to age) for 2 days prior to colonoscopy plus a sodium phosphate (NaP) enema preparation 64 or 128 mL (containing sodium acid phosphate 10% and sodium phosphate 8%) on the morning of the procedure (n=31) in a randomized, single-blind, single-centre study.<sup>[25]</sup> Data reported are for the intent-to-treat population. \*  $p < 0.01$  vs BIS + NaP enema preparation.

laxatives (e.g. bisacodyl, senna); however, electrolyte and fluid disturbances, patient discomfort and poor compliance associated with the use of these preparations prompted the development of alternatives.<sup>[2,5]</sup> Commonly used colorectal cleansing agents currently include enema preparations, magnesium salts (e.g. citrate), oral gastrointestinal lavage regimens, polyethylene glycol and sodium phosphate.<sup>[1,5]</sup> In addition, various adjunctive agents including bisacodyl (which stimulates colonic peristalsis), metoclopramide (which accelerates gastric emptying and intestinal transit), senna extract (which enhances colonic motility) and sodium picosulfate can be added to these colorectal cleansing regimens.<sup>[10,30]</sup>

Oral gastrointestinal lavages, consisting of high volume (7–12 L) saline or balanced electrolyte solutions, have been utilized for cleansing the colon and rectum.<sup>[5,30]</sup> Mannitol, a nonabsorbable sugar, was used in the early formulations (as an osmotic agent) to induce diarrhoea.<sup>[3,5]</sup> However, this preparation (and other non-absorbable carbohydrates) is associated with the production of hydrogen and methane (via fermentation by colonic bacteria), which can cause explosions during electrosurgical procedures.<sup>[3,30,31]</sup> Oral gastrointestinal lavages also have the disadvantage of being associated with poor patient tolerance and dramatic shifts in electrolytes and fluids. These disadvantages have encouraged the development of osmotically balanced solutions formulated to result in minimal water absorption or secretion into the lumen of the colon and rectum.<sup>[5,30]</sup>

Oral polyethylene glycol is an iso-osmotic nonabsorbable lavage solution that induces a minimal net absorption or secretion of water or electrolytes, thereby avoiding significant electrolyte and fluid shifts.<sup>[2,5,30]</sup> However, the large volume (4 L) and the salty taste impinge upon compliance and, therefore, on the effectiveness of the cleansing process.<sup>[2,5,30]</sup> In an effort to improve the taste and smell of polyethylene glycol, a lavage solution without sodium sulfate (and with increased chloride and decreased potassium levels) was developed.<sup>[2,5]</sup> With the absence of sodium sulfate, the mechanism of

action of this agent is dependent upon the osmotic effects of polyethylene glycol.<sup>[5]</sup> A comparison of the sulfate-free polyethylene glycol preparation with a low-dose sodium picosulfate/magnesium citrate preparation (which was not discussed in this review) in two randomized, single-blind studies indicated efficacy, tolerability and patient compliance benefits with the sodium picosulfate/magnesium citrate preparation versus the sulfate-free polyethylene glycol.<sup>[32,33]</sup> Other polyethylene glycol preparations, including a low volume option in combination with oral bisacodyl, have also been developed along with various flavourings to enhance palatability.<sup>[2,5]</sup>

Oral sodium phosphate is a hyperosmotic preparation consisting of monobasic and dibasic sodium phosphate that osmotically draws plasma water into the lumen of the colon to promote cleansing.<sup>[5,30]</sup> Dilution is required prior to administration to prevent vomiting, and significant oral fluids must be consumed in order to prevent dehydration.<sup>[2,5]</sup> Oral magnesium citrate is also a hyperosmotic agent that acts by increasing intraluminal volume and thus intestinal motility, and also by instigating the release of cholecystokinin, which stimulates fluid secretion and increased intestinal motility.<sup>[5,30]</sup>

The combination of sodium picosulfate and magnesium citrate is commonly used as a colorectal cleansing agent in patients prior to various investigational (e.g. colonoscopy) and surgical procedures.<sup>[34]</sup> The sodium picosulfate component increases the frequency and force of peristalsis, resulting in electrolyte and water retention in the colon, which can lead to significant dehydration, hyponatraemia and other electrolyte irregularities and associated complications.<sup>[10,35]</sup>

In adult patients, oral sodium picosulfate/magnesium citrate was generally well accepted and considered pleasant to taste, thus potentially affecting patient compliance (section 4.1). Moreover, this preparation was better accepted than oral polyethylene glycol, as might be expected given the smaller volume to be swallowed (section 4.1). The combination was also better accepted than oral sodium phosphate, although it was not as well accepted as a sodium phosphate enema

preparation (section 4.1). Furthermore, sodium picosulfate/magnesium citrate and oral magnesium citrate were rated as 'pleasant to taste' by a similar proportion of adult patients in both treatment groups.<sup>[21]</sup>

A recent consensus document prepared for the American Society of Colon and Rectal Surgeons, the American Society for Gastrointestinal Endoscopy and the Society for American Gastrointestinal and Endoscopic Surgeons<sup>[5]</sup> recommends the use of either oral polyethylene glycol or oral sodium phosphate, based on the patient's overall health, co-morbid conditions and currently prescribed medications. However, the authors also noted that oral sodium picosulfate/magnesium citrate is available (primarily in the UK) and is as effective as polyethylene glycol in terms of preparation quality but has a better tolerability profile. This efficacy and tolerability profile of sodium picosulfate/magnesium citrate is corroborated by a Canadian Association of Gastroenterology position paper.<sup>[29]</sup> However, a recent meta-analysis concluded that the optimal colorectal cleanser, in terms of efficacy and tolerability, has yet to be determined.<sup>[36]</sup> Furthermore, both the consensus opinion<sup>[5]</sup> and the position paper<sup>[29]</sup> noted that efficacy data comparing sodium picosulfate/magnesium citrate with oral sodium phosphate are conflicting.

Clarification of the relative efficacy of oral sodium picosulfate/magnesium citrate versus oral sodium phosphate was not facilitated by the single study discussed in section 3.1. In this study, similar numbers of patients receiving two sachets of oral sodium picosulfate/magnesium citrate or two 45 mL doses of oral sodium phosphate the day before a double-contrast barium enema procedure achieved satisfactory barium coating and none/minimal faecal residue.<sup>[22]</sup> Therefore, further comparative studies are warranted to accurately determine the relative efficacy of these two colorectal cleansing agents prior to colonoscopy or other exploratory procedures. A single dose of sodium picosulfate/magnesium citrate was less effective than a sodium phosphate enema preparation in two studies in patients undergoing flexible sigmoidoscopy (section 3.1).<sup>[19,20]</sup> How-

ever, these data should be interpreted with caution because the administrative regimen used differed from that recommended (section 5). In several clinical studies in adult patients, sodium picosulfate/magnesium citrate was at least as effective as oral magnesium citrate or oral polyethylene glycol as a colorectal cleansing agent (section 3.1). However, the findings of one of the studies comparing sodium picosulfate/magnesium citrate versus magnesium citrate were not unexpected, given that the regimen in the study by Swarbrick et al.<sup>[21]</sup> of one sachet of magnesium citrate administered at 6pm on the day prior to the procedure differs from the recommended dose of two sachets 6–8 hours apart on the day prior to the procedure.<sup>[26]</sup>

A recent meta-analysis (published as an abstract and poster presentation) of 14 studies (nine of which were randomized and single- or double-blind) in 792 adults, adolescents and children undergoing a barium enema procedure, bowel surgery or colonoscopy found that sodium picosulfate/magnesium citrate was effective as a colorectal cleanser prior to various exploratory or surgical procedures, with 82% of patients achieving at least adequate cleansing.<sup>[37]</sup>

Recent studies have revealed the significant role the timing of administration plays in the quality of colorectal cleansing. While the optimal timing of administration of oral sodium picosulfate/magnesium citrate was not evaluated in the clinical studies discussed in section 3, it may exert considerable influence on the quality of colorectal cleansing and thus requires further investigation.

Limited data showed that oral sodium picosulfate/magnesium citrate was effective (section 3.2) and generally well tolerated (section 4.2) as a colorectal cleansing agent in children and adolescents. In these patients, sodium picosulfate/magnesium citrate was significantly more effective and at least as well tolerated as oral bisacodyl plus a sodium phosphate enema preparation.

Oral sodium picosulfate/magnesium citrate is generally well tolerated in adult patients, with adverse events generally being gastrointestinal in nature (e.g. abdominal cramps/pain) and of mild to moderate intensity (section 4.1). This

combination is at least as well tolerated as oral sodium phosphate or oral polyethylene glycol, with moderate to severe nausea and vomiting occurring less frequently in sodium picosulfate/magnesium citrate recipients than in those receiving oral sodium phosphate, and abdominal bloating/pain and nausea developing less often with sodium picosulfate/magnesium citrate than polyethylene glycol therapy (section 4.1). The incidence of abdominal pain and sleep disturbance in sodium picosulfate/magnesium citrate versus oral magnesium citrate recipients was similar in one study, but significantly lower with sodium picosulfate/magnesium citrate in another. While the incidence of most adverse events was similar in recipients of sodium picosulfate/magnesium citrate and a sodium phosphate enema preparation, more patients receiving sodium picosulfate/magnesium citrate reported moderate/severe flatulence, incontinence and sleep disturbance, and more patients receiving the enema preparation reported rectal soreness (section 4.1). The tolerability profile of sodium picosulfate/magnesium citrate was reportedly similar in patients aged >70 years to that in patients aged <70 years (section 4.1). Sodium picosulfate was also generally well tolerated in those studies included in a recent meta-analysis.<sup>[37]</sup>

Economic considerations are important in the evaluation of a therapeutic intervention. To date, no pharmacoeconomic data evaluating the use of oral sodium picosulfate/magnesium citrate as a colorectal cleanser have been published.

In conclusion, oral sodium picosulfate/magnesium citrate was at least as effective and well tolerated as oral magnesium citrate or oral polyethylene glycol in adult patients undergoing a double-contrast barium enema procedure in three large, randomized, comparative clinical studies. In contrast, sodium picosulfate/magnesium citrate was less effective than a sodium phosphate enema preparation in two studies in patients undergoing flexible sigmoidoscopy. A similar number of patients receiving sodium picosulfate/magnesium citrate or oral sodium phosphate the day before a double-contrast barium enema procedure achieved satisfactory barium coating and none/minimal

faecal residue in one study. However, the data from three of these studies should be interpreted with caution because the administrative regimens used differed from that recommended. Sodium picosulfate/magnesium citrate is also an effective and generally well tolerated colorectal cleansing agent in children and adolescents; the preparation was more effective than oral bisacodyl plus a sodium phosphate enema preparation in this population. Further research is thus required to accurately position sodium picosulfate/magnesium citrate and fully establish its efficacy and tolerability prior to various exploratory or surgical procedures. Nevertheless, oral sodium picosulfate/magnesium citrate provides a useful option in the preparation of the colon and rectum in adults, adolescents and children undergoing any diagnostic procedure (e.g. colonoscopy or x-ray examination) requiring a clean bowel and/or surgery.

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