1 NAME OF THE MEDICINAL PRODUCT
PICOPREP Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains the following active ingredients:

Sodium picosulfate	10.0 mg
Magnesium oxide, light	3.5 g
Citric acid	12.0 g

Each sachet also contains:
Potassium hydrogen carbonate 0.5 g [equivalent to 5 mmol (195 mg) potassium]
Lactose (as a component of the flavour)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for oral solution.
White crystalline powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
To clean the bowel prior to X-ray examination or endoscopy.
To clean the bowel prior to surgery when judged clinically necessary (see section 4.4 regarding open colorectal surgery).

4.2 Posology and method of administration
Posology
Adults (including elderly):
(if the procedure is scheduled for the afternoon, it is recommended that the Split Dosing regimen should be used):

SPLIT DOSING REGIMEN (evening-before and day of the procedure)
The first PICOPREP sachet (see Method of Administration section below for reconstitution guidance) is taken the night before the procedure, and the second is taken the next day, in the morning prior to the procedure.

On the day before the procedure – 1 sachet:
- The first reconstituted sachet is taken in the late afternoon/ evening (e.g. 5:00 to 9:00PM), followed by at least 5 x 250 ml drinks of clear liquids (not only water), spread over several hours

On the day of the procedure – 1 sachet:
- The second reconstituted sachet is taken in the morning (5-9 hours before the procedure), followed by at least 3 x 250 ml drinks of clear liquids (not only water), spread over several hours
- Clear liquids (not only water) may be consumed until 2 hours before the time of the procedure

or

DAY-BEFORE DOSING Regimen (evening-before the procedure only)
The first PICOPREP sachet (see Method of Administration section below for reconstitution guidance) is taken in the afternoon or early evening and the second is taken approximately 6 hours later, the night before the procedure.

On the day before the procedure – 2 sachets:
- The first reconstituted sachet is taken in the afternoon or early evening (e.g. 4:00 to 6:00PM), followed by at least 5 x 250 ml drinks of clear liquids (not only water), spread over several hours

- The second reconstituted sachet is taken in the late evening (e.g., 10:00PM to 12:00AM), followed by at least 3 x 250 ml drinks of clear liquids (not only water), spread over several hours
- Clear liquids (not only water) may be consumed until 2 hours before the time of the procedure.

Method of administration
Route of administration: Oral

A low residue diet is recommended on the day prior to the procedure. A clear liquid diet is recommended on the day of the procedure. To avoid dehydration it is important to follow the liquid intake recommendation as advocated together with the PICOPREP dosing whilst the effects of PICOPREP persist (see section Posology). Apart from the liquid intake together with the treatment regimen (PICOPREP + additional liquids), a normal, thirst driven intake of clear liquids is recommended.

Clear liquids should include a variety of soft drinks, clear soup, tea, coffee (without milk, soy or cream), fruit juice without pulp, and water. Liquid intake should not be restricted to only drinking water.

Directions for reconstitution in adults (including elderly):
Reconstitute the PICOPREP powder right before each administration. Do not prepare the solution in advance. Reconstitute the contents of one sachet in a cup of water (approximately 150ml). Stir for 2-3 minutes, the solution should now become an off-white, cloudy liquid with a faint odour of orange. Drink the solution. If it becomes warm, wait until it cools sufficiently to drink.

Paediatric population:
The safety and efficacy of PICOPREP in paediatric patients has not been established.

4.3 Contraindications
- Hypersensitivity to the active substances or to any excipients listed in section 6.1.
- Congestive cardiac failure
- Gastric retention
- Gastro-intestinal ulceration
- Toxic colitis
- Toxic megacolon
- Ileus
- Nausea and vomiting
- Acute surgical abdominal conditions such as acute appendicitis
- Known or suspected gastro-intestinal obstruction or perforation.
- Severe dehydration
- Rhabdomyolysis
- Hypermagnesemia
- Active inflammatory bowel disease
- In patients with severely reduced renal function, accumulation of magnesium in plasma may occur. Another preparation should be used in such cases.

4.4 Special warnings and precautions for use
Because a clinically relevant benefit of bowel cleansing prior to elective, open colorectal surgery could not be proven, bowel cleansers should only be administered before bowel surgery if clearly needed. The risks of the treatment should be carefully weighed against possible benefits and needs depending on surgical procedures performed.

Advise patients to hydrate adequately before, during, and after the use of PICOPREP. An insufficient or excessive oral intake of water and electrolytes could create clinically significant, deficiencies, particularly in less fit patients. In this regard, patients with low bodyweight, children, the elderly, debilitated individuals and

patients at risk of hypokalaemia or hyponatremia may need particular attention. Prompt corrective action should be taken to restore fluid/electrolyte balance in patients with signs or symptoms of hypokalaemia or hyponatremia.

Drinking only water to replace the fluid losses may lead to electrolyte imbalance which may in severe cases lead to complications such as seizures and coma. In rare cases, PICOPREP can cause severe or life-threatening electrolyte problems or impaired renal function in fragile or debilitated patients.

Care should also be taken in patients with recent gastro-intestinal surgery, renal impairment, heart disease or inflammatory bowel disease.

Use with caution in patients on drugs that might affect water and/or electrolyte balance e.g. diuretics, corticosteroids, lithium (see section 4.5).

PICOPREP may modify the absorption of oral medication and should be used with caution e.g. there have been isolated reports of seizures in patients on antiepileptics, with previously controlled epilepsy (see section 4.5 and 4.8).

Use caution when prescribing PICOPREP for patients with a history of seizures and in patients at risk of seizure, such as patients taking medications that lower the seizure threshold (e.g., tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, patients with known or suspected hyponatremia.

There have been rare reports of serious arrhythmias associated with the use of ionic osmotic laxative products for bowel preparation. Use caution when prescribing PICOPREP for patients at increased risk of arrhythmias (e.g., patients with a history of prolonged QT, uncontrolled arrhythmias, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy).

Osmotic laxatives may produce colonic mucosal aphthous ulcerations and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Concurrent use of additional stimulant laxatives with PICOPREP may increase this risk. The potential for mucosal ulcerations should be considered when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease.

Patients with impaired gag reflex and patients prone to regurgitation or aspiration should exercise caution during the administration of PICOPREP.

The period of bowel cleansing should not exceed 24 hours because longer preparation may increase the risk of water and electrolyte imbalance.

This medicine contains 5 mmol (or 195 mg) potassium per sachet. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

This medicine contains lactose as a component of the flavour. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PICOPREP should not be used as a routine laxative.

4.5 Interaction with other medicinal products and other forms of interaction

The absorption of other orally administered medicines (e.g. anti-epileptics, contraceptives, anti-diabetics, antibiotics) may be decreased during the treatment period (see section 4.4). Oral medication administered within one hour of the start of administration of PICOPREP solution may be flushed from the GI tract and

the medication may not be absorbed. Medicines with the potential to chelate with magnesium (e.g., tetracycline and fluoroquinolone antibiotics, iron, digoxin, chlorpromazine and penicillamine) should be taken at least 2 hours before and not less than 6 hours following administration of PICOPREP.

The efficacy of PICOPREP is lowered by bulk-forming laxatives.

Prior or concomitant use of antibiotics with PICOPREP may reduce efficacy of PICOPREP as conversion of sodium picosulfate to its active metabolite BHPM is mediated by colonic bacteria.

Use caution when prescribing PICOPREP for patients with conditions or who are using medications that increase the risk for fluid and electrolyte disturbances or may increase the risk of seizure, arrhythmias, and prolonged QT in the setting of fluid and electrolyte abnormalities. This includes patients receiving drugs which may be associated with hypokalaemia (such as diuretics or corticosteroids, or drugs where hypokalaemia is a particular risk i.e. cardiac glycosides). Caution is also advised when PICOPREP is used in patients on NSAIDs or drugs known to induce Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, antipsychotic drugs and carbamazepine as these drugs may increase the risk of water retention and/or electrolyte imbalance.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no data with PICOPREP use in pregnant women to determine a drug-associated risk of adverse developmental outcomes.

In animal reproduction studies, no adverse developmental effects were observed in pregnant rats when sodium picosulfate, magnesium oxide, and citric acid were administered orally at doses 1.2 times the recommended human dose based on body surface area during organogenesis.

As picosulfate is a stimulant laxative, for safety measure, it is preferable to avoid the use of PICOPREP during pregnancy.

Breast-feeding

There is insufficient data on the use of PICOPREP in nursing mothers, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PICOPREP and any potential adverse effects on the breastfed infant from PICOPREP.

Fertility

Studies with PICOPREP in animals have shown no impairment of fertility or embryo-fetal toxicity. In studies with sodium picosulfate alone, embryofetal toxicity has been observed in rats and rabbits at very high doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The most common adverse reactions are vomiting, nausea, abdominal pain and headache. Hyponatraemia is rare, but is the most commonly reported serious adverse reaction. Adverse reactions from spontaneous reports are presented by frequency category based on incidence in clinical trials when known. Frequency from spontaneous reports for adverse reactions never observed in clinical trials is based on an algorithm as recommended in the European Commission SmPC guideline, 2009, rev 2.

MedDRA Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10.000 to <1/1000)
Immune system disorder		Anaphylactic reaction, Hypersensitivity	
Metabolism and nutrition disorders	Hypermagnesaemia	Hypokalaemia	Hyponatraemia
Nervous system disorders	Headache	Epilepsy, Generalised tonic-clonic seizure[a], Seizure[b], Loss of or depressed level of consciousness Syncope Dizziness Confusional state including Disorientation	Presyncope
Gastrointestinal disorders	Vomiting, Nausea, Abdominal pain	Diarrhoea[c]	Ileal ulcers[d] Anal incontinence[e], Proctalgia
Skin and subcutaneous tissue disorders		Rash (including erythematous rash, maculo-papular rash, urticaria, purpura)	

[a] Defined as grand mal convulsion in previous MedDRA versions. In epileptic patients, there have been isolated reports of seizure/generalised tonic-clonic seizure without associated hyponatraemia.
[b] Defined as convulsions in previous MedDRA versions.
[c] Isolated cases of severe diarrhoea have been reported post-marketing.
[d] Isolated cases of mild reversible aphthoid ileal ulcers have been reported.
[e] Defined as faecal incontinence in previous MedDRA versions.

4.9 Overdose
Overdose would lead to profuse diarrhoea. Treatment is by general supportive measures and correction of fluid and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Contact Laxatives
ATC code: A06A B58

5.1 Pharmacodynamic properties

Mechanism of action
Sodium picosulfate is hydrolyzed by colonic bacteria to form an active metabolite: bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), which acts directly on the colonic mucosa to stimulate colonic peristalsis.

Magnesium oxide and citric acid react to create magnesium citrate in solution, which is an osmotic agent that causes water to be retained within the gastrointestinal tract.

Pharmacodynamic effects
The stimulant laxative activity of sodium picosulfate together with the osmotic laxative activity of magnesium citrate produces a purgative effect which, when ingested with additional fluids, produces watery diarrhea that clear the bowel.

The product is not intended for use as a routine laxative.

5.2 Pharmacokinetic properties

Absorption

Sodium picosulfate, which is a prodrug, is converted to its active metabolite, BHPM, by colonic bacteria.

After administration of 2 sachets of PICOPREP separated by 6 hours, in 16 healthy subjects, sodium picosulfate reached a mean Cmax of 3.2 ng/mL at a median 8 hours (Tmax). After the first sachet, the corresponding value was 2.3 ng/mL at 2 hours. Magnesium oxide and citric acid react in solution to create magnesium citrate. Magnesium concentration value not corrected for baseline were 0.88 and 0.95 mmol/L at 4 and 10 hours, respectively. The baseline value was 0.75 mmol/L.

Distribution

The apparent volume (V/F) of sodium picosulfate was 3910 liters.

Biotransformation and Elimination

The fraction of the sodium picosulfate dose excreted unchanged in urine was 0.11%. Plasma levels of BHPM were low with 13 out of 16 subjects studied having plasma BHPM concentrations below the lower limit of quantification (0.1 ng/mL). Urinary samples show that the majority of excreted BHPM was in the glucuronide-conjugated form. The apparent clearance (CL/F) of sodium picosulfate was 463 L/h. The terminal half-life of sodium picosulfate was 7.4 hours.

Clinical studies in bowel cleansing before colonoscopy have shown an increase from baseline to colonoscopy visit in serum magnesium of approximately 0.11 mmol/L (from 0.86 to 0.97 mmol/L). All changes in serum magnesium were transient and within normal limits, including in patients with mild to moderate renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

Due to the very short treatment duration no long-term studies in animals have been performed.

Reproductive studies have shown no potential for impairment of fertility or harm to the foetus for sodium picosulfate and PICOPREP.

In an animal study on pre- and postnatal development, the NOAEL of PICOPREP was the mid dose of 750 mg/kg BID. The adverse effect that occurred in the 2000 mg/kg BID group (approximately 8 times the recommended human dose), was pup mortality, between lactation days 2 to 4 due to maternal toxicity.

Effects in reproductive and developmental toxicity studies in animals with sodium picosulfate alone were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium hydrogen carbonate
Sodium saccharin
Natural, spray dried orange flavour which contains acacia gum, lactose, ascorbic acid and butylated hydroxyanisole

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years. Once the sachet has been opened, use immediately and discard any unused powder or solution.

6.4 Special precautions for storage
Store below 30°C in the original package in order to protect from moisture.

6.5 Nature and contents of container and special equipment for use
Sachet:4 layers: paper – low density polyethylene – aluminium – thermofusible resin.

PICOPREP is supplied in packages of 2 sachets.

6.6 Special precautions for disposal and other handling
No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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