NAME OF THE MEDICINAL PRODUCT
PICOPREP® Powder for Oral Solution

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

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

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

PHARMACEUTICAL FORM
Powder for oral solution in sachet.
White crystalline powder.

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 Special Warnings and Precautions for Use regarding open colorectal surgery).

POSOLOGY AND METHOD OF ADMINISTRATION
Method of administration
Route of administration: Oral

A low residue diet is recommended on the day prior to the hospital 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 fruit juice without pulp, soft drinks, clear soup, tea, coffee (without milk, soy or cream) and water. Do not drink only water.

Posology
Directions for reconstitution:
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.

Adults (including the elderly):
(if the procedure is scheduled for the afternoon, it is recommended that the Split-Dose regimen should be used):

Split-Dose Regimen (evening-before and day of the procedure)
The first PICOPREP® sachet 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 evening (e.g. 5:00 to 9:00PM), followed by at least five 250 ml drinks of clear liquids, 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 three 250 ml drinks of clear liquids, spread over several hours
- Clear liquids may be consumed until 2 hours before the time of the procedure

or

Day-Before Regimen (evening-before the procedure only)

The first PICOPREP® sachet 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 five 250 ml drinks of clear liquids, 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 three 250 ml drinks of clear liquids, spread over several hours
- Clear liquids may be consumed until 2 hours before the time of the procedure

Paediatric population:

The safety and efficacy of PICOPREP® in paediatric patients has not been established.

CONTRAINDICATIONS

- Hypersensitivity to any of the ingredients of the product
- 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.

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.

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 Interaction with Other Medicinal Products and Other Forms of Interactions).

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, 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.

PICOPREP® may modify the absorption of regularly prescribed 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 Interaction with Other Medicinal Products and Other Forms of Interactions and Undesirable Effects).

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

As a purgative, PICOPREP® increases the gastrointestinal transit rate. The absorption of other orally administered medicines (e.g. anti-epileptics, contraceptives, anti-diabetics, antibiotics) may therefore be modified during the treatment period (see section Special Warnings and Precautions for Use). 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. Tetracycline and fluoroquinolone antibiotics, iron, digoxin, chlorpromazine and penicillamine, should be taken at least 2 hours before and not less than 6 hours after administration of PICOPREP® to avoid chelation with magnesium.

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 angiotensin converting enzyme inhibitors, angiotensin receptor blockers, 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.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

For PICOPREP® no clinical data on exposed pregnancy are available. Studies in animals have shown reproductive toxicity. As picosulfate is a stimulant laxative, for safety measure, it is preferable to avoid the use of PICOPREP® during pregnancy.

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 Preclinical Safety Data).

Breastfeeding

There is no experience with the use of PICOPREP® in nursing mothers. It is not known whether this drug is excreted in human milk. It is advised to exercise caution when PICOPREP® is administered to a nursing woman.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not applicable.

UNDESIRABLE EFFECTS

The most frequent adverse reactions seen in clinical trials are nausea, headache and vomiting.

MedDRA Organ Class	**Common (≥1/100 to ≤1/10)**	**Uncommon (≥1/1000 to ≤1/100)**	**Not known (cannot be estimated from the available data)**
Immune system disorder		Anaphylactic reaction, hypersensitivity	
Metabolism and nutrition disorders		Hyponatraemia and hypokalaemia	
Nervous system disorders	Headache	Epilepsy, grand mal convulsion, convulsions, confusional state	

Gastrointestinal disorders	Nausea and proctalgia	Vomiting, abdominal pain, aphthoid ileal ulcers*	Diarrhoea, faecal incontinence
Skin and subcutaneous tissue disorders		Rash (including erythematous and maculo-papular rash, urticaria, purpura)	

*Isolated cases of mild reversible aphthoid ileal ulcers have been reported.

The frequencies of the side effects are based on post-marketing experience.

Diarrhoea and faecal incontinence are the primary clinical effect of PICOPREP®. Isolated cases of severe diarrhoea have been reported post-marketing.

Hyponatraemia has been reported with or without associated convulsions. In epileptic patients, there have been isolated reports of seizure/grand mal convulsion without associated hyponatraemia.

There have been isolated reports of anaphylactoid reaction.

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

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Contact Laxatives
ATC code: A06A B58

The active components of PICOPREP® are sodium picosulfate and magnesium citrate. Sodium picosulfate is a locally acting stimulant cathartic, which after bacterial cleavage in the colon forms the active laxative compound, bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), which has a dual-action with stimulation of the mucosa of both the large intestine and of the rectum. Magnesium citrate acts as an osmotic laxative by retaining moisture in the colon. The combined action of the two substances is of a 'washing out' effect combined with peristaltic stimulation to clear the bowel.

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

PHARMACOKINETIC PROPERTIES
Sodium picosulfate and magnesium citrate, the two components of PICOPREP®, are locally active, with minimal systemic exposure.

After administration of PICOPREP® (2 sachets separated by 6 hours), picosulfate reached a mean levels of 2.3 and 3.2 ng/mL (C_{max}) at a median of 2 and 8 hours (T_{max}) after the first and second sachet, respectively. The corresponding values for magnesium were 0.88 and 0.95 mmol/L at 4 and 10 hours, respectively. The baseline value was 0.75 mmol/L.

The mean terminal half-life of picosulfate was 7.4 hours. The fraction of the sodium picosulfate dose excreted unchanged in urine was 0.11%. Plasma levels of BHPM were consistently low or undetectable and urinary samples showed that the majority of excreted BHPM was the glucuronide-conjugated form.

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.

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 a 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 with sodium picosulfate alone were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

INCOMPATIBILITIES
Not applicable.

SHELF-LIFE
3 years. Once the sachet has been opened, use immediately and discard any unused powder or solution.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Store in the original package in order to protect from moisture.

NATURE AND CONTENTS OF CONTAINER
Sachet:
4 layers: paper – low density polyethylene – aluminium – thermofusible resin.

PICOPREP® is supplied in packages of 2 sachets.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
No special requirements.

MANUFACTURER
Ferring Pharmaceuticals (China) Co., Ltd.
China

DATE OF REVISION
2 August 2017