1. NAME OF THE MEDICINAL PRODUCT

PICOSTIVE POWDER FOR ORAL SOLUTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains:

Sodium Picosulfate	10.0mg
Magnesium oxide, heavy	3.5g
Citric acid, anhydrous	12.0g

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Description: Powder: White, odourless powder packed in sachet for oral solution.
Reconstituted solution: The reconstituted solution is off-white, cloudy liquid after 2-3 minutes of stirring and becomes a clear solution within 20 minutes in approximately 150 mL.

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 Special Warnings and Precautions for Use regarding open colorectal surgery)

4.2. Posology and method of administration

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults:

Split-Dose Dosing Regimen (Preferred Method)

The Split-Dose regimen is the preferred dosing method. Instruct patients to take two separate doses in conjunction with fluids, as follows:
• Take the first dose during the evening before the procedure (e.g., 5:00 to 9:00 PM) followed by five 250 ml drinks (upper line on the dosing cup) of clear liquids before bed. Consume clear liquids within 5 hours.
• Take second dose, the next day approximately 5 hours before the procedure followed by at least three 250 ml drinks of clear liquids before the procedure. Consume clear liquids within 5 hours up until 2 hour before the time of the procedure.

Day-Before Dosing Regimen (Alternative Method)

The Day-Before regimen is the alternative dosing method for patients for whom the Split-Dosing is inappropriate. Instruct patients to take two separate doses in conjunction with fluids, as follows:
• Take the first dose in the afternoon or early evening (e.g., 4:00 to 6:00 PM) before the procedure followed by five 250 ml drinks (upper line on the dosing cup) of clear liquids before the next dose. Consume clear liquids within 5 hours.
• Take the second dose approximately 6 hours later in the late evening (e.g., 10:00 PM to 12:00 AM), the night before the procedure followed by three 250 ml drinks of clear liquids before bed. Consume clear liquids within 5 hours.

Children:

The first dose reconstituted in water as directed, taken before 8 am on the day before the procedure. Second dose 6 to 8 hours later.
1 - 2 years: ¼ sachet morning, ¼ sachet afternoon
2 - 4 years: ½ sachet morning, ½ sachet afternoon
4 - 9 years: 1 sachet morning, ½ sachet afternoon
9 and above: adult dose

Route of administration: Oral
Sodium Picosulfate, supplied as a powder, must be reconstituted with cold water right before its use. There are two dosing regimens, each requires two separate dosing times:
• The preferred method is the "Split-Dose" method and consists of two separate doses: the first dose during the evening before the procedure and the second dose the next day, during the morning prior to the procedure.
• The alternative method is the "Day Before" method and consists of two separate doses: the first dose during the afternoon or early evening before the procedure and the second dose 6 hours later during the evening before the procedure.

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 Sodium Picosulfate dosing whilst the effects of Sodium Picosulfate persist. Apart from the liquid intake together with the treatment regimen (Sodium Picosulfate + 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.

Additional fluids must be consumed after every dose in both regimens up until 2 hours before the time of the procedure. Instruct patients that if they experience severe bloating, distention, or abdominal pain following the first dose, delay the second dose until their symptoms resolve.

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

Directions for reconstitution for children under 9 years old dosing:
(a) Reconstitute the Sodium Picosulfate powder right before each administration. Do not prepare the solution in advance.
(b) Reconstitute the contents of one sachet in a cup of water (approximately 200 ml).
(c) Stir for 2-3 minutes, the solution should now become off-white, cloudy liquid with a faint odour of orange. Take ¼ or ½ of the solution according to the dosing regimen. If it becomes warm, wait until it cools sufficiently to drink.

4.3. Contra-indications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Congestive cardiac failure
- Gastric retention
- Gastro-intestinal ulceration
- Toxic colitis
- Toxic megacolon
- Ileus
- Severe 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 Special 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.

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 body weight, 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.

Care should also be taken in patients with recent gastro-intestinal surgery as well as 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 Interaction with Other Medicaments and Other Forms of Interactions).

Picostive 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 4.5 and 4.8).

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

For an early time of the day procedure it may be required to take the second dose during the night and possible sleep disturbance may occur.

This medicine contains potassium in the sachet. This should be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

Picostive should not be used as a routine laxative.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

As a purgative, Sodium picosulfate 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 4.4). 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 Picostive to avoid chelation with magnesium.

The efficacy of Sodium picosulfate is lowered by bulk-forming laxatives.

Care should be taken with patients already 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 Sodium picosulfate is used in patients on NSAIDs or drugs known to induce 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. Pregnancy and Lactation

Pregnancy

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

Fertility

Studies 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. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Breastfeeding

There is no experience with the use of Picostive in nursing mothers, so the drug should only be used in nursing mothers if clearly needed.

4.7. Effects on Ability to Drive and Use Machines

Not Relevant

4.8. Undesirable Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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 Picostive. 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 anaphylactic reaction.

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

5.1. Pharmacodynamics

Pharmacotherapeutic group: Contact Laxatives
ATC code: A06A B58
The active components of Picostive 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.

Clinical efficacy and safety
The dosing regimen as described in section 4.2 Posology, and herein further referred to as the tailored dosing regimen, was investigated and evaluated in trial 000121 (OPTIMA) that compared the efficacy, safety and tolerability of Sodium picosulfate administered according to the tailored dosing regimen versus the fixed schedule of dosing (i.e. first dose is taken before 8am and second dose is taken 6-8 hours later on the day before procedure), called day before dosing regimen (204 patients were randomized, 131 received tailored dosing, 73 received day before dosing).

Superiority of the tailored dosing regimen was demonstrated compared to the day before dosing regimen in overall colon cleansing and responder status for ascending colon cleansing. For overall colon cleansing, the tailored dosing regimen was compared to the day before dosing regimen, based on the treatment difference in mean total Ottawa Scale score (4.26 versus 8.19 in mean total Ottawa scale score for tailored dosing regimen and day before dosing regimen respectively, with a corresponding p-value <0.0001, for the Intend to Treat (ITT) analysis set). For the responder status of the ascending colon, the proportion of patients with an Ottawa Scale score of either 0 (excellent) or 1 (good), was compared between the tailored dosing regimen and the day before dosing regimen. Patients randomized to the tailored dosing regimen were observed to have a 4.05 greater chance of being a responder with respect to ascending colon cleansing compared to patients randomized to the day before dosing regimen.

Endpoint	**Endpoint Study Population (n=204)**	**Sodium picosulfate day before dosing regimen estimate (n=73)**	**Sodium picosulfate tailored dosing regimen estimate (95%CI) (n=131)**
Mean Total Ottawa Scale Score (Adjusted estimate)	ITT	8.19	4.26 -3.93(-4.99, -2.87) p-value < 0.0001
Proportion of patients with an Ottawa Scale score of either 0 (excellent) or 1 (good)	ITT	15.1	61.1% RD* 0.46 (0.34; 0.58) RR** 4.05 (2.31; 7.11)

* Absolute Risk Difference (Crude)
** Relative Risk (Crude)

5.2. Pharmacokinetic Properties

Both active components are locally active in the colon, and neither are absorbed in any detectable amounts.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose anhydrous
Polyvinyl pyrollidone
Potassium carbonate
Sucralose

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

Please refer to expiry date on the outer box.

6.4. Special Precautions for Storage

Keep this medicine out of the sight and reach of children. Store below 30°C.
Do not use this medicine after the expiry date which is stated on the carton and sachet. The expiry date refers to the last day of that month.

6.5. Nature and Contents of Container

Powder for Oral Solution is packed in printed four layer laminated paper foil sachets. Such 2 sachets are packed in a carton along with Package Insert.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

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