COMPANY CORE DATA SHEET
No. 0094-08

LAXOBERON®
Sodium picosulphate

COMPOSITION

1 ml (= 15 drops) contains 7.5 mg
excipients**:
drops: sodium benzoate, sorbitol solution 70%, sodium citrate dehydrate, citric acid monohydrate, water purified

Excipient with known effect:

This medicinal product contains approx. 450 mg sorbitol per 1 mL (please refer to "Special warnings and precautions").

INDICATIONS

For use in cases of constipation and in conditions which require defecation to be facilitated.

DOSAGE AND ADMINISTRATION

The following dosages are recommended to be taken at night to produce evacuation the following morning.

It is recommended to start with the lowest dose. The dose may be adjusted up to the maximum recommended dose to produce regular stools.
The maximum recommended daily dose should not be exceeded.

Drops 7.5 mg/1 mL (= 15 drops)

Adults:	10 - 20 drops (5 - 10 mg) per day
Pediatric population	
Children > 10 years:	10 - 20 drops (5 - 10 mg) per day
Children aged 4 - 10 years:	5 - 10 drops (2.5 - 5 mg) per day

CONTRAINDICATIONS

LAXOBERON® is contraindicated in patients with

- ileus, or intestinal obstruction
- Severe painful and/or feverish acute abdominal conditions (e.g. appendicitis) potentially associated with nausea and vomiting.
- Acute inflammatory bowel diseases.
- Severe dehydration.
- Known hypersensitivity to sodium picosulphate or any other component of the product.

- In case of Rare hereditary conditions that may be incompatible with an excipient of the product (please refer to “Special warnings and precautions”).

Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

SPECIAL WARNINGS AND PRECAUTIONS

As with all laxatives, LAXOBERON® should not be taken on a continuous daily basis or for extended periods without investigating the cause of constipation. Prolonged excessive use may lead to fluid and electrolyte imbalance and hypokalaemia.

Dizziness and/or syncope have been reported in patients who have taken LAXOBERON®. The details available for these cases suggest that the events would be consistent with defecation syncope (or syncope attributable to straining at stool), or with a vasovagal response to abdominal pain related to the constipation, and not necessarily to the administration of sodium picosulphate itself.

Children should not take LAXOBERON® without medical advice.

Excipients:
Drops 7.5 mg/1 mL
1 mL drops contain 0.45 g sorbitol, resulting in 0.6 g sorbitol per maximum recommended daily dose for treatment of adults and children > 10 years. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.
LAXOBERON® drops contains less than 1 mmol sodium (23 mg) per 10 mL, that is to say essentially ‘sodium-free’.

INTERACTIONS

The concomitant use of diuretics or adreno-corticosteroids may increase the risk of electrolyte imbalance if excessive doses of LAXOBERON® are taken.

Electrolyte imbalance may lead to increased sensitivity to cardiac glycosides.

Concurrent administration of antibiotics may reduce the laxative action of LAXOBERON®.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Long experience has shown no evidence of undesirable or damaging effects during pregnancy.

Nevertheless, as with all drugs, LAXOBERON® should only be taken during pregnancy on medical advice.

Lactation
Clinical data show that neither the active moiety of sodium picosulphate BHPM (bis-(p-hydroxyphenyl)-pyridyl-2-methane) nor its glucuronides are excreted into the milk of healthy lactating human females.

Thus, LAXOBERON® can be used during breast-feeding.

Fertility
No studies on the effect on human fertility have been conducted. Non-clinical studies did not reveal any effect on fertility (please refer to “Toxicology”).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that due to a vasovagal response (e.g., to abdominal spasm) they may experience dizziness and/or syncope. If patients experience abdominal spasm they should avoid potentially hazardous tasks such as driving or operating machinery.

SIDE EFFECTS

Immune system disorders
Hypersensitivity.

Nervous system disorders
Dizziness, syncope.
Dizziness and syncope occurring after taking sodium picosulphate appear to be consistent with a vasovagal response (e.g.,to abdominal spasm, defecation).

Gastrointestinal disorders
Abdominal cramps, abdominal pain, diarrhoea, vomiting, nausea, abdominal discomfort.

Skin and subcutaneous tissue disorders
Skin reactions such as angioedema , drug eruption , rash , pruritus.

OVERDOSE

Symptoms
If high doses are taken watery stools (diarrhoea), abdominal cramps and a clinically significant loss of fluid, potassium and other electrolytes can occur.

Furthermore cases of colonic mucosal ischaemia have been reported in association with doses of LAXOBERON® considerably higher than those recommended for the routine management of constipation.

LAXOBERON®, as with other laxatives, when taken in chronic overdose may cause chronic diarrhoea, abdominal pain, hypokalaemia, secondary hyperaldosteronism and renal calculi. Renal tubular damage, metabolic alkalosis and muscle weakness secondary to hypokalaemia have also been described in association with chronic laxative abuse.

Therapy
After the ingestion of LAXOBERON® absorption can be minimised or prevented by inducing

vomiting or gastric lavage. Replacement of fluids and correction of electrolyte imbalance may be required. This is especially important in the elderly and the young.
Administration of antispasmodics may be of some value.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Laxative
ATC code: A06AB08

Sodium picosulphate, the active ingredient of LAXOBERON®, is a locally acting laxative from the triarylmethane group, which, after bacterial cleavage in the colon stimulates the mucosa of the large intestine, causing colonic peristalsis and promotes accumulation of water,and consequently electrolytes, in the colonic lumen. This results in a stimulation of defecation, reduction of transit time and softening of the stool.

As a laxative that acts on the colon, sodium picosulphate specifically stimulates the natural evacuation process in the lower region of the gastrointestinal tract. Therefore, sodium picosulphate is ineffective in altering the digestion or absorption of calories or essential nutrients in the small intestine.

PHARMACOKINETICS

Absorption and Distribution
After oral ingestion, sodium picosulphate reaches the colon without any appreciable absorption. Therefore, enterohepatic circulation is avoided.

Biotransformation
Sodium picosulphate is converted into the active laxative compound, bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), via bacterial cleavage in the distal segment of the intestine.

Elimination
Following conversion, only small amounts of BHPM are absorbed and are almost completely conjugated in the intestinal wall and the liver to form the inactive BHPM glucuronide. After oral administration of 10 mg sodium picosulphate 10.4% of the total dose was excreted as BHPM glucuronide in urine after 48 hours.
In general, urinary excretion decreases when higher doses of sodium picosulphate are being administered.

Pharmacokinetic/Pharmacodynamic relationship(s)
Consequently, the onset of action of the preparation is usually between 6 - 12 hours, which is determined by the release of the active substance (BHPM).
There is no direct or inverse relationship between the laxative effect and plasma levels of the active moiety.

TOXICOLOGY

Sodium picosulphate showed low acute toxicity in laboratory animals. The oral LD_{50}-values were >17 g/kg (mouse), >16 g/kg (rat) and >6 g/kg (rabbit, dog), respectively. Major signs of toxicity were polydipsia, piloerection, diarrhoea and vomiting, respectively .

Subchronic and chronic toxicity studies up to 6 months in rats (up to 100 mg/kg) and dogs (up to 1000 mg/kg) with sodium picosulphate induced diarrhoea and body weight loss when given at dose levels higher than 500 and 5000 times the therapeutic dose in man (on a 50 kg basis). Following high-level exposure singular atrophy of the gastrointestinal mucosa occurred. The treatment-related changes were caused by the chronic intestinal irritation associated with cachexia. All toxic effects were reversible. Sodium picosulphate had no adverse effects on heart rate, blood pressure and respiration in conscious and anaesthetised animals.

Sodium picosulphate was free of any genotoxic potential in bacteria and mammalian cells under *in vitro* and *in vivo* conditions. No conventional chronic bioassays for carcinogenicity in rats and mice are available.

Sodium picosulphate was investigated for teratogenicity (Segment II) in rats (1, 10, 1000 and 10000 mg/kg) and rabbits (1, 10 and 1000 mg/kg) following oral dosing. Maternal toxic dose levels causing severe diarrhoea were associated with embryotoxicity (increase of early resorptions) without any teratogenic effects or adverse effects on the reproductive performance of the offspring. Fertility and general embryonic development (Segment I) as well as pre- and postnatal development (Segment III) of rats were not impaired by oral doses of 1, 10 and 100 mg/kg.

In summary, due to the low bioavailability following oral exposure, the acute and chronic toxicity of sodium picosulphate is low .

AVAILABILITY

Bottle of 10 ml Reg.No.
Store below 30° C.
Store in a safe place, out of the reach of children.

Only on doctor's prescription.
Harus dengan resep dokter.

Manufactured by:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia

For:
PT. Aventis Pharma, Jakarta, Indonesia