

Exhibit D

Approved (Translated) Label in Brazil

(7.5 mg/ml drops; 2.5 mg capsules)

English Translation by:

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São Paulo/SP

Brazil

GUTTALAX®
sodium Picosulphate
7,5 mg/ml

This package insert has been continuously updated. Please read it before using the medicine.

Pharmaceutical forms and presentation

Oral solution: Bottle with 20 ml.

Other pharmaceutical form and presentation

Gelatinous pearls: package with 30 and 50 pearls

Adult and pediatric use

Composition

Each ml (= 15 drops) contains:

sodium picosulphate.....7,5mg

Excipients: methylparaben sodium, sorbitol, hydrochloric acid, purified water

Information to the patient

GUTTALAX is a contact laxative for the treatment of constipation. The active ingredient, sodium picosulphate, stimulates the functioning of the intestine, providing an efficient and soft effect.

Keep the medicine in room temperature (15°C to 30°C). Protect from light and humidity.. The shelf-life of the product is 36 months. Do not take medicines after the expiry date. Inform your physician if pregnancy occurs during the treatment or after it. Inform your physician if you are breast-feeding. Abdominal discomfort and diarrhea may occur as adverse reactions, especially if high doses are taken. If severe undesirable reactions occur, a physician should be consulted. **All medicines should be kept out of the reach of children.**

GUTTALAX should not be used in patients with acute inflammatory disorders of the gastrointestinal tract. Do not use the product for long periods without the knowledge of your physician. Special restrictions or precautions for the use of the product in over 65 years old patients are unknown. Do not use the product without medical

advice during pregnancy. Breast-feeding women should not use GUTTALAX.

Do not take medicines without the knowledge of your physician. It may be dangerous to your health.

Technical Information

Sodium picosulphate, the active ingredient of GUTTALAX, is a locally acting laxative of the triarylmethane group, which after bacterial cleavage in the colon stimulates the mucosa of the large intestine, causing colonic peristalsis. Thus, after a latency period related with individual sensitivity and dose, it determines bowel emptying.

After oral administration, sodium picosulfate reaches the colon without any appreciable absorption, thus avoiding enterohepatic circulation. By bacterial cleavage in the colon it is converted in its active form, the free diphenol. Consequently, there is an onset of action after 6 to 12 hours, which is determined by the release of the active substance.

After administration, only small amounts of the drug are systematically available. Urinary excretion reflects low systemic burden after oral administration. There is no relationship between the laxative effect and plasmatic levels of the active diphenol.

The acute oral toxicity of sodium picosulphate was investigated in mice, rats and rabbits, and was >17 g/kg, >16 g/kg and >6 g/kg, respectively. Main signs of toxicity in mice and rats were polydipsia, piloerection and diarrhoea. Rabbits were the less sensitive from all animal species tested.

Subchronic and chronic studies up to 6 months in rats and dogs with sodium picosulphate at dose levels higher than 1000 times the therapeutic dose in man. Induced diarrhoea and body weight loss. Following high-level dose 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 showed no effects on heart rate, blood pressure and respiration in conscious and anaesthetised animals.

Sodium picosulfate did not show any mutagenic potential. No chronic bioassays for carcinogenicity are available.

Sodium picosulphate was investigated on its effect on fertility/segment I (treatment before mating up to implantation), teratogenicity/segment II (exposure during organogenesis) and peri- and postnatal development/segment III (treatment late gestation II). Dose levels were 1, 10 and 100 mg/kg body weight. Maternal toxic

dose levels causing severe diarrhoea were associated with embryotoxicity (increase of early resorption) without any teratogenic effect or adverse effect on the reproductive performance of the offspring.

Indications

For the treatment of constipation and in conditions which require defecation to be facilitated.

Contraindications

GUTTALAX is contraindicated in patients with ileus, intestinal obstruction, acute surgical abdominal condition such as acute appendicitis, acute inflammatory bowel diseases and in cases of serious dehydration. GUTTALAX is also contraindicated in patients with known hypersensitivity to sodium picosulphate or to any other formula component.

Precautions

As with all laxatives, GUTTALAX should not be taken daily without interruption, for long periods. If laxatives are needed every day, the cause of constipation should be investigated. Prolonged or excessive use may cause an electrolytic imbalance and hypokalemia, and may precipitate onset of rebound constipation. Children should not take GUTTALAX without medical advice.

Pregnancy and Lactation

Long experience with GUTTALAX has shown no evidence of undisireable or damaging effects during pregnancy. Nevertheless, as with all drugs, GUTTALAX should only be administered during pregnancy under strict medical prescription. Even though investigatons have shown that sodium picosulphate does not enter breast milk, breast feeding during the use of the product is not recommended.

Drug Interactions

The concomitant use of diuretics or adreno-corticosteroids may increase the risk of electrolytic imbalance, if excessive doses of the product are taken. Electrolytic imbalance may cause increased sensitivity to cardiac glycosides.

Adverse Reactions

Episodes of abdominal discomfort, abdominal cramps and abdominal pain may occur. Diarrhoea has been reported. Isolated cases of allergic reactions, including skin reactions and angio-oedema, have been reported in association with the administration of GUTTALAX

Dosage and Administration

Unless otherwise prescribed by the physician, the following dosages are recommended:

Adults and children over 10 years: 10 to 20 drops (5-10 mg)

Children from 4 to 10 years: 5 to 10 drops (2,5 - 5 mg)

For children under 4 years of age, the recommended dose is 0,25 mg /kg of body weight.

It is recommended to take GUTTALAX at night to produce evacuation in the following morning.

FOLLOW CORRECTLY THE INSTRUCTIONS OF USE; IF SYMPTOMS PERSIST, A PHYSICIAN SHOULD BE CONSULTED.

The bottle of GUTTALAX is provided with a modern dropper, which is easy to handle: just put the bottle in vertical position and let the desired quantity of drops fall down.

1. Open the cap.
2. Turn the bottle
3. In vertical position, in order to make the drops fall, beat the bottom of the bottle lightly with your finger.

Overdosage

Symptoms

If high doses of GUTTALAX are taken, diarrhoea abdominal cramps and a significant loss of potassium loss as well as other Electrolytes may occur.

Furthermore, cases of colonic mucosal ischemia have been reported in association with doses of GUTTALAX considerably higher than those recommended for the routine management of constipation.

Laxatives in chronic overdose are known to cause chronic diarrhoea, abdominal

pain, hypokalaemia, secondary hyperaldosteronism and renal calculi. Renal tubular damage, metabolic alkalosis and secondary muscle weakness have also been described.

Treatment

After ingestion of GUTTALAX, absorption may be minimised or prevented by gastric lavage or inducing vomiting. Replacement of fluids and correction of electrolytic balance may be necessary. This measure is particularly important with older patients, as well as with the younger ones. Administration of antispasmodics may be useful.

Batch no., manufacturing date, expiring date: see package.

For your safety, keep this package until the medicament is totally consumed.

MS-1.0367.0075

Techn. Resp.: Farm. Laura M. S. Ramos - CRF-SP nº 6870

Boehringer Ingelheim do Brasil Química e Farmacêutica Ltda.
Rod. Regis Bittencourt (BR 116), km 286
Itapeceira da Serra-SP

SAC ☎ 0800-7016633

CNPJ/MF nº 60.831.658/0021-10

Made in Brazil

BPI 0094-03 20030527

GUTTALAX®
sodium picosulphate

Pharmaceutical form and presentation

Gelatinous pearls: Package with 30 and 50 pearls

Other pharmaceutical form and presentation

Oral solution: 20 ml vial

Adult and pediatric use

Composition

Each gelatinous pearl contains:

sodium picosulphate.....2,5mg

(corresponding to 2,593 monohydrated sodium picosulphate)

Excipients: propyleneglicol, macrogol, desionized water

Information to the patient

GUTTALAX is a contact laxative indicated for the treatment of constipation. The active ingredient, sodium picosulphate, stimulates the functioning of the intestine, providing an efficient and soft effect.

Keep the medicine in room temperature (15°C to 30°C). Protect from light and humidity. The shelf life of the product is 30 months. Do not take medicines after the expiry date. Inform your physician if pregnancy occurs during the treatment or after it. Inform your physician if you are breast-feeding. Abdominal discomfort and diarrhea may occur as adverse reactions, especially if high doses are taken. If severe undesirable reactions occur, a physician should be consulted.

All medicines should be kept out of the reach of children.

GUTTALAX should not be used in patients with acute inflammatory disorders of the gastrointestinal tract. Do not use the product for long periods without the knowledge of your physician. Special restrictions or precautions for the use of the product in over 65 years old patients are unknown. Do not use the product without medical advice during pregnancy. Breast-feeding women should not use GUTTALAX.

Do not take medicines without the knowledge of your physician. It may be dangerous to your health.

Technical Information

Sodium picosulphate, the active ingredient of GUTTALAX, is a locally acting laxative of the triarylmethane group, which, after bacterial cleavage in the colon, stimulates the mucosa of the large intestine, causing colonic peristalsis.

After oral administration, sodium picosulphate reaches the colon without any appreciable absorption, thus avoiding enterohepatic circulation. By bacterial cleavage in the colon it is converted in its active form, the free diphenol. Consequently, there is an onset of action after 6 to 12 hours, which is determined by the release of the active substance.

After administration, only small amounts of the drug are systematically available. Urinary excretion reflects low systemic burden after oral administration. There is no relationship between the laxative effect and plasmatic levels of the active diphenol.

The acute oral toxicity of sodium picosulphate was investigated in mice, rats and rabbits, and was >17 g/kg, >16 g/kg and >6 g/kg, respectively. Main signs of toxicity in mice and rats were polydipsia, piloerection and diarrhoea. Rabbits were the less sensitive from all animal species tested.

Subchronic and chronic studies up to 6 months in rats and dogs with sodium picosulphate at dose levels as high as 1000 times the therapeutic dose in man. Induced diarrhoea and body weight loss. Following high-level dose 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 showed no effects on heart rate, blood pressure and respiration in conscious and anaesthetised animals.

Sodium picosulphate did not show any mutagenic potential. No chronic bioassays for carcinogenicity are available.

Sodium picosulphate was investigated on its effect on fertility/segment I (treatment before mating up to implantation), teratogenicity/segment II (exposure during organogenesis) and peri- and postnatal development/segment III (treatment late gestation through lactation, in rats and rabbits – only segment II). Dose levels were 1, 10 and 100 mg/kg body weight. Maternal toxic dose levels causing severe diarrhoea were associated with embryotoxicity (increase of early resorption) without any teratogenic effect or adverse effect on the reproductive performance of the offspring.

Indications

For the treatment of constipation and in conditions which require defecation to be facilitated.

Contraindications

GUTTALAX is contraindicated in patients with ileus, intestinal obstruction, acute surgical abdominal condition such as acute appendicitis, acute inflammatory bowel diseases and in cases of serious dehydration. GUTTALAX is also contraindicated in patients with known hypersensitivity to sodium picosulphate or to any other formula component.

Precautions

As with all laxatives, GUTTALAX should not be taken daily without interruption, for long periods. If laxatives are needed every day, the cause of constipation should be investigated. Prolonged or excessive use may cause a electrolytic imbalance and hypokalemia, and may precipitate onset of rebound constipation. Children should not take GUTTALAX without medical advice.

Pregnancy and Lactation

Long experience with GUTTALAX has shown no evidence of undesirable or damaging effects during pregnancy. Nevertheless, as with all drugs, GUTTALAX should only be administered during pregnancy on strict medical prescription. Even though investigations have shown that sodium picosulphate does not enter breast milk, the use of the product is not recommended during lactation.

Drug Interactions

The concomitant use of diuretics or adreno-corticosteroids may increase the risk of electrolytic imbalance, if excessive doses of the product are taken. Electrolytic imbalance may cause increased sensitivity to cardiac glucosides.

Adverse Reactions

Episodes of abdominal discomfort, abdominal cramps and abdominal pain may occur. Diarrhoea has been reported. Isolated cases of allergic reactions, including

skin reactions and angio-oedema, have been reported in association with the administration of GUTTALAX.

Dosage and Administration

Unless otherwise prescribed by the physician, the following dosages are recommended:

Adults and children over 10 years:

2 to 4 gelatinous pearls (5-10 mg)

Children from 4 to 10 years:

1 to 2 gelatinous pearls (2,5 - 5mg)

For children under 4 years, the recommended dose is 0,25 mg/kg of body weight.

GUTTALAX taken at night with liquid, can produce evacuation in the following morning. Depending on the convenience and daily routine, the pearls can be administered on alternative hours, remembering that its effect occurs at about 6 - 12 hours after the administration. It is possible to swallow the pearls without concomitant liquid due to the reduced size and gelatinous composition.

Follow correctly the instructions of use; if symptoms persist, a physician should be consulted.

Overdosage

Symptoms

If high doses of GUTTALAX are taken, diarrhoea, abdominal cramps and a significant loss of potassium as well as other electrolytes may occur.

Furthermore, cases of colonic mucosal ischemia have been reported in association with doses of GUTTALAX considerably higher than those recommended for the routine management of constipation.

Laxatives in chronic overdose are known to cause chronic diarrhoea, secondary hyperaldosteronism and renal calculi. Renal tubular damage, metabolic alkalosis and muscle weakness secondary to hypokalaemia have also been described.

Treatment

After ingestion of GUTTALAX, absorption may be minimised or prevented by gastric lavage or inducing vomiting. Replacement of fluids and correction of electrolytic

balance may be necessary. This measure is particularly important with older patients, as well as with the younger ones. Administration of antiespasmotics may be useful.

Batch no., manufacturing date, expiring date: see package.

For your safety, keep this package until the medicament is totally consumed.

MS-1.0367.0075

Manufactured and packaged by:
Cardinal Health Italy 407 S.p.A.
Aprilia, LT – Itália

Imported and distributed by:

Boehringer Ingelheim do Brasil Química e Farmacêutica Ltda.
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