LAEVULOSA 5 %
Solution for injection

**Composition**

<table>
<thead>
<tr>
<th>LAEVULOSA 5 %</th>
<th>Laevulose - 5 %, 277.8 mmol/l</th>
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<tbody>
<tr>
<td>Water for Injection</td>
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**Action**

The active substance of **LAEVULOSA infusion solution** (ÅØÑ - B05BA) is Laevulose (Diabetin, Fructose, Fruit Sugar, D-Fructopyranose) - a monosaccharide, containing small quantities of glucose and water. It is sweeter than sucrose and sorbitol and about the same as xylitol. Laevulose is a source of carbohydrate calories, similar to dextrose, it restores blood glucose levels, minimizes liver glycogen depletion and exerts a protein-sparing action. It is utilised more rapidly than dextrose in both diabetics and non-diabetics, being metabolised or converted into glycogen in the absence of insulin. It may be employed similarly to dextrose by intravenous infusion in conditions associated with carbohydrate insufficiency. The dosage is determined in accordance with the condition and needs of the patient. Laevulose should be administered slowly; the maximum rate of infusion should not exceed 800 mg per kg body weight per hour.

From studies in patients with various non-metabolic disorders and in cirrhotic patients, it was shown that laevulose, infused intravenously, increases the renal excretion of pyruvate; glucose does not do this. The increased renal excretion is mainly due to depression of the tubular resorption of pyruvate. In most cases it causes within an hour of administration of the sugar, and its extent depends on the infusion rate.

Studies on the utilisation of laevulose by patients with diabetes led to the following conclusions.

- Although laevulose is rapidly utilised even after prolonged administration, the rate is much slower than in a healthy person;
- It results in weight gain, decrease in the need for insulin, and improvement in the patient's general metabolic condition;
- It is devoid of dangers. For acidosis, and renal and myocardial impairment secondary to diabetes, laevulose may be given intravenously provided that the rate of administration is checked to avoid reaching the renal threshold too quickly. Laevulose is used as an alternative to glucose in parenteral nutrition, except in diabetic patients, is not recommended because of the risk of lactic acidosis and uric blood level elevations. It is not useful for the treatment of hypoglycaemia. Laevulose has antiketogenic action, decreases the non-specific free fat acids, but in a less extent than glucose. It has no osmodiureic action after rapid and concentrated infusion rate in the body.

Pharmacodynamics:
Laevulose undergoes oxidation to carbon dioxide and water. Unlike dextrose, fructose does not require insulin for phosphorylation and conversion to glucose, acting in glucose metabolic cycle, readily converted to glycogen; and oral and an intravenous infusion of fructose produces lower serum glucose levels and less glucosuria than similar doses of dextrose or sorbitol.

Pharmakinetics:
Laevulose is rapidly absorbed (though more slowly than glucose) from the gastrointestinal tract. Metabolized mainly in the liver where it causes increased lactate formation, high-energy phosphate depletion, increased uric acid formation and inhibition of protein synthesis. Thus resulting in increased concentration of blood lactate and serum uric acid. After oral ingestion of laevulose, 80 to 90 % is absorbed as laevulose in the jejunum by facilitated diffusion. The intestinal absorption of laevulose may be decreased during exercise. Insulin is not required for transport of laevulose into the cell, laevulose can enter the cell to the part of glycolytic pathway. Laevulose is more readily converted to glycogen than dextrose. Laevulose is metabolized by insulin-independent pathways in the liver, intestinal wall, kidney and adipose tissue. Any excess quantity of laevulose (over 300 g/day) is excreted in the urine. About 5 % of laevulose is excreted via urine (3 - 9 %), which should be in mind when calories intake is calculated.

Indications
Introduction of water and laevulose as energy source: parental nutrition with laevulose, alone or in combination with other carbohydrates, aminoacids and oil emulsions; parental nutrition in diabetes, stress, starvation; liver diseases, hepatitis; intoxications; uremic coma; cardiac and vascular diseases and hypertonic dehydration.

**Contraindications:**
Laevulose may be fatal or cause growth retardation if administered to patients with hereditary fructose tolerance. Do not prescribe at cases with methanol intoxication; inborn intolerance to Laevulose; do not use neither by hypoglycemia nor for dilution of Thiopental.

**Special precautions and warnings:**
1. Lactic acid is the major product of laevulose metabolism and laevulose should be used with caution in patients with hepatic disease or in patients with pre-existing acidosis.
2. Laevulose may increase the serum level of uric acid and should not be administered to patients with gout.
3. Use laevulose with caution in patients with diabetes mellitus or impaired renal function.
4. Rapid infusion (500 mL/hr) of large quantities of laevulose may raise serum uric acid levels, or cause epigastric or substernal pain or discomfort, or cramping and abdominal pain.
5. Monitor clinical and laboratory status periodically to evaluate fluid balance, electrolyte concentrations and acid-base balance. Use caution to prevent overhydration and electrolyte abnormalities.
6. Hypokalemia may occur with excessive administration of potassium-free fructose solutions.

**Use during pregnancy and breast-feeding**
There is no data for teratogenic and embritotoxic action. The preparation must be applied under strong indications only by the physician’s prescription in pregnant and breast-feeding women.

**Effects on ability to drive a motor vehicle or operate machinery**
No data for a negative effect of the preparation on motor ability and CNS (central nerve system).

**Interactions with other medicaments and other forms of interaction:**
At intravenous infusions of laevulose with different drugs an important condition for the therapy is the possibility for combination at concomitant administration.
The following drugs are applied concomitantly with laevulose solutions with proved physico-chemical compatibilities.
- Albumin
- Calcium (calcium gluconate)
- Chloramphenicol
- Chlorthiazide
- Chlorpromazine
- Cimetidine
- Dimenhydrinate
- Ephedrine
- Epinephrine
- Gentamicine - 120 mg/l in laevulose 5 % physically compatible and gentamicin bioactivity stable for 24 hours at 25°C
- Heparin
- Hydrocortisone
- Mezlocillin
- Moxalactam
- Neostigmine
- Netilmicin
- Oxacillin
- Oxytetracyclin
- Oxytocine
- Papaverine

**Incompatibilities of combinations between laevulose and following drugs are observed:**
- Αminocapronic acid.
- Ampicillin (20 g/l è laevulose 5 %).
- Hydralazine - colour change reported
- Thiopental (incompatible with solution of laevulose 1 hour after preparing)
- Warfarin (incompatible with solution of laevulose 1 hour after preparing)

**Administration and dosage:**

Laevulose is applied as water solutions with different concentrations. Dose of laevulose is dependent upon patient’s age, weight and clinical condition (see table 1). Any excess quantity (over 300 g/day) is excreted in the urine.

<table>
<thead>
<tr>
<th>Children</th>
<th>5 % (200 kcal)</th>
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<tbody>
<tr>
<td>0-6 months</td>
<td>12g/kg/24h (1720-1920ml)</td>
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<tr>
<td>6-12 months</td>
<td>10g/kg/24h (1600-2000ml)</td>
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<tr>
<td>1-3 years</td>
<td>8 g/kg/24h (1920-2440ml)</td>
</tr>
<tr>
<td>4-8 years</td>
<td>6 g/kg/24h (1920-3120ml)</td>
</tr>
<tr>
<td>9-14 years</td>
<td>3 g/kg/24h (1480-3000ml)</td>
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<tr>
<td>Adults</td>
<td>30-40 kcal/kg/24h</td>
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</tbody>
</table>

By maximal dose is recommended after introduction of 1/2 volume an interval of 2 hours in order to preclude any blood-chemical changes. By completely parenteral nutrition use **LAEOLOSA - infusion solution** in combination with aminoacids.

**Overdosage:**

There is no data.

**Undesirable effects:**

*CARDIOVASCULAR* - after fluid of laevulose solutions congestive states, and peripheral edema or pulmonary edema with dyspnea may occur.

*ENDOCRINE/METABOLIC* - patients with pre-existing acidosis may be further compromised with laevulose administration since lactic acid is the major product of laevulose metabolism. Lactic acidosis has occurred following laevulose...
Infusion of laevulose at a rate of 1 g/kg/h causes a rise in blood lactate concentration of 1 to 5 mEq/l followed by a fall in blood pH and bicarbonate. After excessive administration of potassium-free solutions hypokalemia may occur. Adverse effects from hypophosphatemia after laevulose administration have been reported. Laevulose causes hyperuricemia and may increase the serum level of uric acid and should not be administered to patients with gout. Rapid infusion (500 mL/hr) of large quantities of laevulose may raise serum uric acid levels.

LIPID METABOLISM - Twelve hyperinsulinemic, carbohydrate sensitive men and 12 men with normal responses were fed diets containing 0 %, 7.5 %, and 15 % laevulose for 5 weeks in a cross-over design study. Results revealed higher systolic blood pressures, higher total plasma cholesterol’s and higher low-density lipoprotein (LDL) cholesterol after the men consumed 7.5 % and 15 % laevulose diets. Plasma triglycerides increased significantly as laevulose in the diets of the hyperinsulinemics increased, but was not affected in the controls. Other long-term studies with normal human subjects, juvenile or adult insulin treated diabetic patients, and hypertriglyceridemic patients found no increase in plasma triglyceride levels with laevulose administration.

Pharmaceutical form:
Infusion solution of 500 ml.

Storage:
Store in dry places, protected from light, at a temperature of 15 to 30º C.

Expiry term:
3 (three) years of the manufacture date.