

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Laevolac

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml contain 3.3 g lactulose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution

Clear colorless to pale brownish yellow, viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Constipation.
- Acute and chronic hepatic encephalopathy.

4.2 Posology and method of administration

The lactulose solution may be administered diluted or undiluted. The dose should be titrated according to the clinical response. Lactulose may be given as a single daily dose or up to three divided daily doses, using the measuring cup.

A single dose of lactulose should be swallowed in one and should not be kept in the mouth for an extended period of time.

The posology should be adjusted according to the individual needs of the patient. The starting dose can be adjusted after adequate treatment effect individually (maintenance dose). Several days (2-3 days) of treatment may be needed in some patients before adequate treatment effect occurs. In case of single daily dose, this should be taken at the same time of the day, e.g. during breakfast. During the therapy with laxatives, it is recommended to drink sufficient amounts of fluids (1.5-2 l/day, equal to 6-8 glasses).

Constipation

After a few days the starting dosage may be adjusted to the maintenance dose based upon treatment response. Several days (2-3 days) of treatment may be needed before treatment effect occurs.

	Starting dose	Maintenance dose
Adults and adolescents	15 - 30 ml	15 - 30 ml
Children (7 - 14 years)	15 ml	10 - 15 ml
Children (1 - 6 years)	5 - 10 ml	5 - 10 ml
infants under 1 year	Up to 5 ml	Up to 5 ml

If diarrhoea occurs, the dosing regimen should be reduced.

Treatment of portal systemic encephalopathy - for adults only:

Beginning with 30 - 50 ml 3 times daily (corresponding to 60 - 100 g Lactulose).
The dosage has to be adopted to get 2-3 soft stools daily, pH of the stools should be between 5.0 to 5.5.

Children:

The safety and efficacy in children aged 0 - 18 years has not been established. No data are available.

In elderly patients and patients with renal or hepatic insufficiency no special dosage recommendations exist.

Duration of treatment

The duration of treatment has to be adopted according to the symptoms.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Use in patients with galactosaemia.
- Acute inflammatory bowel disease (ulcerative colitis, Crohn's disease), gastrointestinal obstruction or subocclusive syndromes, digestive perforation or risk of digestive perforation, painful abdominal syndromes of undetermined cause.

4.4 Special warnings and precautions for use

In case of insufficient therapeutic effect after several days consultation of a physician is advised.

From the route of synthesis Lactulose may contain traces of sugars (Not more than 67 mg/ml lactose, 100 mg/ml galactose, 67 mg/ml epilactose, 27 mg/ml Tagatose and 7 mg/ml Fructose). Lactulose should be administered with care to patients who are intolerant to lactose.

The dose normally used in constipation should not pose a problem for diabetics.

However, higher doses used for treatment of portal systemic encephalopathy may need to be taken into considerations for diabetics. 15 ml of Lactulose contain 42,7 KJ (10,2 kcal) = 0,21 bu.

The defecation reflex may be altered during the treatment with lactulose.

Patients with rare hereditary problems of galactose or fructose intolerance, lactase deficiency or glucose-galactose mal-absorption should not take this medicine.

For patients with gastro-cardiac syndrome (Roemheld syndrome) lactulose should only be taken after consultation of a physician. If symptoms like meteorism or bloating occur in such patients after lactulose intake, the dose should be reduced, or the treatment should be discontinued.

Chronic use of unadjusted doses and misuse can lead to diarrhoea and disturbance of the electrolyte balance.

For elderly patients or patients that are in bad general condition and who take lactulose for a more than 6 months period, periodic control of electrolytes is indicated.

In patients with portal systemic encephalopathy, concomitant administration of other laxatives should be avoided, because it hinders the individualization of drug dose. Furthermore, for the patients referred above, it should be taken into account the chance of causing electrolyte imbalance and, mainly, hypokalaemia that could aggravate encephalopathy.

During the therapy with laxatives it is recommended to drink sufficient amounts of fluids (1.5-2 l/day, equal to 6-8 glasses).

Paediatric population

Use of laxatives in children should be exceptional and under medical supervision.

Lactulose should be administered with caution in infants and small children with autosomal recessive hereditary fructose intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

Lactulose may increase the loss of potassium induced by other drugs (e.g. thiazides, steroids and amphotericin B). Concomitant use of cardiac glycosides can increase the effect of the glycosides through potassium deficiency.

With increasing dosage, a decrease of pH-value in the colon is found. Therefore, drugs which are released in the colon pH-dependently (e.g. 5-ASA) can be inactivated.

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited data on pregnant patients indicate no malformative nor foeto/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

The use of lactulose may be considered during pregnancy if necessary.

Breastfeeding

Lactulose can be used during breastfeeding.

Fertility

For Lactulose no clinical data on the effects on fertility are available.

4.7 Effects on ability to drive and use machines

Lactulose has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects

Flatulence may occur during the first few days of treatment. As a rule, it disappears after a couple of days. When dosages higher than instructed are used, abdominal pain and diarrhoea may occur. In such a case the dosage should be decreased.

Gastrointestinal disorders

Very common ($\geq 1/10$): Flatulence, abdominal pain,
Common ($\geq 1/100 < 1/10$): nausea and vomiting; if dosed too high, diarrhoea.

Investigations

Electrolyte imbalance due to diarrhoea.

Immune system disorders

Not known (frequency cannot be estimated from the available data): hypersensitivity reactions

Skin and subcutaneous tissue disorders

Not known (frequency cannot be estimated from the available data): rash, pruritus, urticaria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>

4.9 Overdose

If the dose is too high, the following may occur:

Symptom: diarrhoea and abdominal pain.

Treatment: cessation of treatment or dose reduction. Extensive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Osmotically acting laxatives.

ATC code: A06A D11

Lactulose is a synthetic disaccharide formed from D-galactose and fructose. In the colon lactulose is metabolised by bacterial enzymes to short chained fatty acids mainly lactic and acetic acid as well as methane and hydrogen. This effect leads to a decrease of the pH-value and an increase of the osmotic pressure in the colon. This causes stimulation of peristalsis and an increase of the water content of the faeces.

In higher dosage lactulose causes a reduction of the pH-value, which results in an increased H⁺-concentration and a shift from NH₃ (absorbable) to NH₄⁺ (non-absorbable). The nitrogen excretion in the stool is accelerated. This effect may be used in the treatment of hyperammonaemia. In the treatment of hepatic encephalopathy lactulose reduces the concentration of NH₃ in the blood by about 25-50 %.

Lower pH in the colon leads to suppression of proteolytic bacteria, which are involved in the formation of ammonia. Decrease in pH is caused by increasing the content of acidophilic bacteria (eg Lactobacillus). Reduced pH and the osmotic effect cleanse the colon; this stimulates the bacteria to use ammonia for bacterial protein synthesis.

5.2 Pharmacokinetic properties

Lactulose is practically not absorbed, because in man there is no corresponding disaccharidase available in the upper intestinal tract. Not being absorbed as such, it reaches the colon unchanged. There it is metabolised by the colonic bacterial flora. Metabolism is complete at doses up to 25-50 g or 40-75 ml; at higher dosages, a proportion may be excreted unchanged.

5.3 Preclinical safety data

Preclinical data based on studies of single and repeated dose toxicity reveal no special hazards for humans. A long-term animal study does not give reference to tumorigenic potential. Lactulose was not teratogenic in mice, rats and rabbits. After oral administration systemic

toxicity is not to be expected due to the pharmacological and pharmacokinetic properties of lactulose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening – 12 months, and no later than the expiration date on the package.

6.4 Special precautions for storage

Store below 25°C.

Keep container tightly closed.

6.5 Nature and contents of container

Brown PET bottles containing 300 ml, or 500 ml with a polyethylene child resistant screw cap.

For the bottles as measuring device a measuring cup (polypropylene) with filling marks is added.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. LICENSE HOLDER

Megapharm Ltd.

15 Ha'tidhar street, Ra'anana, Israel.

8. MANUFACTURER

Fresenius Kabi Austria GmbH

Hafnerstrasse 36

8055 Graz, Austria

9. ISRAEL LICENSE NUMBER

115-98-29714

10. This leaflet was Revised in May 2023 according to MOHs guidelines.