COMPANY CORE DATA SHEET
Lactulose

Date of approval: 17 AUG 2016 Date of previous approval: 30 APR 2015

1. NAME OF THE MEDICINAL PRODUCT

Trademark, 667 g/l, oral solution
Trademark Fruit, 667 g/l, oral solution
Trademark, 95 %, oral powder
Trademark, 10g, oral powder

Lactulose is authorized as
Duphalac, Bifiteral, Betulac, Lactulose Biphar, Lactecon, Duphalac dry, Bifiteral dry, Duphalac Fruit, Avilac.

Trademark, 10 g, oral powder, is authorized as Laktipex.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trademark oral solution contains 667 g lactulose per 1000 ml.

Trademark Fruit oral solution contains 667 g lactulose per 1000 ml flavoured with plum aroma.

One 15 ml sachet contains 10 g lactulose.

Trademark oral powder contains lactulose (> 95%).
Trademark, 10 g, oral powder: 1 sachet contains 10 g lactulose.

For a full list of excipients, see section ‘List of excipients’.

3. PHARMACEUTICAL FORM

Oral solution.
A clear, viscous liquid, colourless to brownish yellow.

Oral solution flavoured with plum aroma.
A clear, viscous liquid, colourless to brownish yellow.

Powder for oral administration.
White to almost white, crystalline powder.

Trademark, 10 g, oral powder:
Oral powder, sachet

4. CLINICAL PARTICULARS

COMPANY CORE DATA SHEET
Lactulose

Date of approval: 17 AUG 2016 Date of previous approval: 30 APR 2015

4.1 Therapeutic indications

- Constipation: regulation of the physiological rhythm of the colon
- Where a soft stool is considered of medical benefit (haemorrhoids, post colonic/anal surgery)
- Hepatic encephalopathy (HE): treatment and prevention of hepatic coma or precoma

4.2 Posology and method of administration

The lactulose solution may be administered diluted or undiluted.

The posology should be adjusted according to the individual needs of the patient.

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

In case of single daily dose, this should be taken at the same time, e.g. during breakfast.

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

Trademark oral powder can be taken from a spoon or tipped directly onto the tongue and then washed down with a drink of water or fluid. The crystals may also be sprinkled on food or mixed with water or fluids before swallowing; disperse the powder through the fluid while stirring.

For Trademark in bottles the measuring cup may be used.

For Trademark in 15 ml single dose sachets the corner of the sachet should be torn off and contents taken immediately.

<u>Dosing in constipation or where a soft stool is considered of medical benefit</u>
Lactulose may be given as a single daily dose or in two divided doses, for Trademark in bottles the measuring cup may be used.

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.

Trademark oral solution in bottles or 15 ml single dose sachets:

COMPANY CORE DATA SHEET
Lactulose

Date of approval: 17 AUG 2016 Date of previous approval: 30 APR 2015

	Starting dose daily	Maintenance dose daily
Adults and adolescents	15-45 ml, corresponding to 1-3 sachets	15-30 ml, corresponding to 1-2 sachets
Children (7-14 years)	15 ml, corresponding to 1 sachet	10-15 ml, corresponding to 1 sachet*
Children (1-6 years)	5-10 ml	5-10 ml
Infants under 1 year	up to 5 ml	up to 5 ml

* If the maintenance dose is below 15 ml, Trademark in bottles should be used.

For a precise dosing for infants and children up to 7 years Trademark in bottles should be used.

Trademark oral powder:

	Starting dose daily	Maintenance dose daily
Adults and adolescents	10-30 grams	10-20 grams
Children (7-14 years)	10 grams	7-10 grams
Children (1-6 years)	3-7 grams	3-7 grams
Infants under 1 year	up to 3 grams	up to 3 grams

Dosing in HE (for adults only)

For oral administration:
Starting dose: 3 to 4 times daily 20-30 g (2-3 sachets) or 30-45 ml (2-3 sachets).
This dose may be adjusted to the maintenance dose to achieve 2 to 3 soft stools per day.

For rectal administration:

In acute cases (impending coma or coma stage) Trademark may be administered as a retention enema (300ml Trademark/700ml water). The enema is to be retained for 30-60 minutes; the procedure is to be repeated every 4-6 hrs until oral medication can be administered.

Paediatric population
The safety and efficacy in children (newborn to 18 years of age) with HE have not been established. No data are available.

Elderly patients and patients with renal or hepatic insufficiency
No special dosage recommendations exist, since systemic exposure to lactulose is negligible.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the ingredients.
- Galactosaemia
- Gastrointestinal obstruction, digestive perforation or risk of digestive perforation

4.4 Special warnings and precautions for use

Consultation of a physician is advised in case of:
- Painful abdominal symptoms of undetermined cause before the treatment is started
- Insufficient therapeutic effect after several days.

Lactulose should be administered with care to patients who are intolerant to lactose (see section 'List of excipients')

The dose normally used in constipation should not pose a problem for diabetics. The dose used in the treatment of HE is usually much higher and may need to be taken into consideration for diabetics.

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

This product contains lactose, galactose and small amounts of fructose. Therefore, patients with the rare hereditary problem of galactose or fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

When administered as a retention enema, due to the strong cathartic effect, fecal incontinence, bedsoiling, and peri-anal irritation due to the acidic stool can be expected. The hydration status of the patient should be observed carefully.

Trademark Fruit* contains 0.4 vol % ethanol (alcohol), i.e. up to 160 mg per dose, equivalent to 4 ml beer, 2 ml wine per dose. Harmful for those suffering from alcoholism**. To be taken into account in pregnant or breast feeding women, children and high-risk groups such as patients with liver disease, or epilepsy**.

Paediatric population
Use of laxatives in children should be exceptional and under medical supervision.
It should be taken into account that the defaecation reflex could be disturbed during the treatment.

* [Note: some Trademark Fruit may not have alcohol containing flavor]
** [Note: warnings and precautions can be removed for the Trademark Fruit without alcohol]

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

Pregnancy

No effects during pregnancy are anticipated, since systemic exposure to lactulose is negligible.

Trademark can be used during pregnancy.

Trademark Fruit* contains 0.4 vol % ethanol (alcohol). To be taken into account in pregnant women**.

Lactation

No effects on the breastfed newborn/infant are anticipated, since the systemic exposure of the breast-feeding woman to lactulose is negligible.

Trademark can be used during breast-feeding.

Trademark Fruit* contains 0.4 vol % ethanol (alcohol). To be taken into account in breast-feeding women**.

Fertility

No effects are to be expected, since systemic exposure to lactulose is negligible.

* [Note: some Trademark Fruit may not have alcohol containing flavor]
** [Note: warnings and precautions can be removed for the Trademark Fruit without alcohol]

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

Summary of the safety profile
Flatulence may occur during the first few days of treatment. As a rule it disappears after a few days.

When dosages higher than instructed are used, abdominal pain and diarrhea may occur. In such a case the dosage should be decreased.

If high doses (normally only associated with hepatic encephalopathy, HE) are used for an extended period of time, the patient may experience an electrolyte imbalance due to diarrhea.

Tabulated list of adverse reactions
The following undesirable effects have been experienced with the below indicated frequencies in lactulose-treated patients in placebo-controlled clinical trials [very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)].

MedDRA SOC	Frequency category			
	Very common	**Common**	**Uncommon**	**Rare**
Gastrointestinal disorders	Diarrhea	Flatulence, abdominal pain, nausea, vomiting		
Investigations			Electrolyte imbalance due to diarrhea	

Paediatric population
The safety profile in children is expected to be similar as in adults.

4.9 Overdose

If the dose is too high, the following may occur:
Symptom: diarrhea and abdominal pain.
Treatment: cessation of treatment or dose reduction. Extensive fluid loss by diarrhea or vomiting may require correction of electrolyte disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Osmotically acting laxatives, ATC code: A 06A D11

In the colon lactulose is broken down by colonic bacteria into low-molecular organic acids. These acids lead to a lowering of pH in the colonic lumen and via an osmotic effect to an increase of the volume of the colonic contents. These effects stimulate the peristalsis of the colon and return the consistency of the stools. The constipation is cleared and the physiological rhythm of the colon is reinstated.

In hepatic encephalopathy (HE), the effect has been attributed to suppression of proteolytic bacteria by an increase of acidophilic bacteria (e.g. lactobacillus), trapping of ammonia in the ionic form by acidification of the colonic contents, catharsis due to the low pH in the colon as well as an osmotic effect, and alteration of the bacterial nitrogen metabolism by stimulating the bacteria to utilize ammonia for bacterial protein synthesis.
Within this context, however, it should be realized that hyperammonemia alone cannot explain the neuropsychiatric manifestations of HE. The ammonia however might serve as a model compound for other nitrogenous substances.

Lactulose as a prebiotic substance strengthens the growth of health promoting bacteria, like Bifidobacterium and Lactobacillus, whereas potentially pathogenic bacteria, like Clostridium and Escherichia coli may be suppressed.
This may lead to a more favorable balance of the intestinal flora.

5.2 Pharmacokinetic properties

Lactulose is poorly absorbed after oral administration and 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

The results of acute, sub-chronic and chronic toxicity studies in various species indicate that the compound has very low toxicity. The effects observed, appear to be more related to the effect of bulk in the gastrointestinal tract than to a more specific toxic activity.

In reproduction and teratology experiments in rabbits, rats or mice no adverse effects were found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trademark oral solution and Trademark oral powder do not contain any excipients, but may contain small amounts of related sugars (e.g. lactose, galactose, epilactose, fructose) from the route of synthesis.

Trademark Fruit* oral solution contains plum aroma and no further excipients.
The plum aroma contains ethanol (alcohol*).

Trademark Fruit may contain small amounts of related sugars (e.g. lactose, galactose, epilactose, fructose) from the route of synthesis.

* [Note: some Trademark Fruit may not have alcohol containing flavor]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

In accordance with national approved registration file.

6.4 Special precautions for storage

In accordance with national approved registration file.

6.5 Nature and contents of container

In accordance with national approved registration file.

6.6 Special precautions for disposal

In accordance with national approved registration file.