SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lactulose Solution BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of solution contains Lactulose 3.35 g.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

A clear, viscous liquid, colourless or pale brownish yellow, miscible with water.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Constipation, hepatic encephalopathy (portal systemic encephalopathy).

4.2 Posology and method of administration

Posology
The lactulose solution may be administered diluted or undiluted. Each dose may if necessary be taken with fruit juice, water or milk, etc., to increase palatability.

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).

If diarrhoea occurs, the dosing regimen should be reduced.

Constipation

Paediatric population
Starting dose

Children 5 to 10 years:	10ml twice daily
Children under 5 years:	5ml twice daily
Infants under 1 year:	2.5ml twice daily

Adults: initially 15ml twice daily. Dosage can often be gradually reduced to 10-20ml a day or every other day.

Elderly: lactulose has been shown to be a suitable laxative for use in the elderly at the standard adult dose.

Hepatic encephalopathy

Children: Not recommended for treatment of children (newborn to 18 years of age).

Adults: initially 30 – 50ml (6 – 10 x 5ml spoonfuls) three times daily
Dosage should be adjusted to produce two or three soft stools daily and an acidic faecal pH.

Elderly: the standard adult dose is recommended

Because of the physiological mode of action of lactulose it may take up to 48 hours before effects are obtained. However, clinical experience has shown that this medicament does exhibit a "carry-over" effect which may enable the patient to reduce the effective dose gradually over a period of time.

Method of administration
For oral administration only

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- 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

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.

This product contains lactose, galactose and small amounts of fructose. (Not more than 67 mg/ml lactose, 100 mg/ml galactose, 67 mg/ml epilactose, 27 mg/ml tagatose and 7 mg/ml fructose).
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose - galactose malabsorption should not take this medicine.

Long term use of this product is inadvisable except under medical supervision. The product contains a small amount of lactose (0.3 g/5 ml), therefore it should be used with caution in patients who are lactose intolerant.

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.

Lactulose may contain more than 5 g lactose/galactose/epilactose depending upon the dose taken. This should be taken into account in patients with diabetes mellitus.
15 ml of Lactulose contain 42.7 KJ (10.2 kcals) = 0.21 BU.

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

The dose used in the treatment of hepatic encephalopathy is usually much higher and may need to be taken into consideration for diabetics.

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 take lactulose for a more than 6 months period, periodic control of electrolytes is indicated.

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 administrated with caution in infants and small children with autosomal recessive hereditary fructose intolerance.

It should be taken into account that the defaecation reflex could be disturbed during the treatment.

4.5 Interactions 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.

The elimination of certain colonic bacteria by broad spectrum anti-infective agents may interfere with the degradation of lactulose and prevent the acidification of colonic contents.

4.6 Fertility, pregnancy and lactation

Pregnancy
No effects during pregnancy are anticipated, since systemic exposure to lactulose is negligible. Limited data on pregnant patients indicate neither 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. Lactulose Solution BP can be used during pregnancy, if necessary.

Breast-feeding
No effects on the breastfed new-born/infant are anticipated since the systemic exposure of the breast-feeding woman to lactulose is negligible. Lactulose Solution BP can be used during breast-feeding, if necessary.

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

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 the event of diarrhoea, adequate fluid intake should be maintained during treatment and the dosage reduced to prevent loss of fluid and potassium, and exacerbation of encephalopathy. See also overdose section 4.9.
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 diarrhoea. Dosage should then be adjusted to obtain two or three formed stools per day.

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**
Gastrointestinal disorders	Flatulence, abdominal pain,	Diarrhoea, nausea, vomiting
Investigations		Electrolyte imbalance due to diarrhoea

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

If the dose is too high, the following may occur: diarrhoea and abdominal pain.

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

There is no specific antidote and symptomatic treatment should be given if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Osmotically acting laxatives, ATC code: A06AD11

Lactulose is a synthetic disaccharide formed from D-galactose and fructose. Lactulose as a prebiotic substance strengthens the growth of bifidobacteria and lactobacilli, whereas Clostridium and Escherichia coli may be suppressed. There is no enzyme in the gastro-intestinal area capable of hydrolysing this disaccharide. In the colon lactulose is broken down by the colonic bacteria to low molecular weight organic acids (mainly lactic acid and acetic acid) as well as methane and hydrogen that produce an increased osmotic pressure and slightly acidify (lower the pH) the colonic contents, causing stimulation of peristalsis and an increase in stool water and stool softening.

Furthermore since the colonic contents are then more acid than blood, ammonia can be expected to migrate from the blood into the colon. In the acidic environment NH3 is converted to (NH4)+, trapping it and preventing its absorption. This is what makes lactulose useful in hepatic encephalopathy.

5.2 Pharmacokinetic Properties

Lactulose is poorly absorbed after oral administration as there is no corresponding disaccharidase available in the upper intestinal tract 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.

Urinary excretion has been determined to be 3% or less, and is virtually complete within 24 hours when lactulose given orally. Lactulose does not exert its effect until it reaches the colon. Therefore 24 to 48 hours may be required to produce normal bowel movement.

5.3 Preclinical Safety Data

Preclinical data of acute and chronic toxicity studies on human indicate that the compound has no special health hazard. A long-term animal study does not give reference to tumorigenic potential. Teratogenic studies in rabbits, rats or mice no adverse effects were found.

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

No added excipients. Lactulose Solution BP may however contain the following related substances:

Galactose	nmt 15.0% of the lactulose content	(0.5025g/5ml)
Lactose	nmt 10.0% of the lactulose content	(0.335g/5ml)
Epilactose	nmt 10.0% of the lactulose content	(0.335g/5ml)
Tagatose	nmt 4.0% of the lactulose content	(0.134g/5ml)
Fructose	nmt 1.0% of the lactulose content	(0.0335g/5ml)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Store in the original container.

Dilution and subsequent storage not recommended.

6.5 Nature and contents of container

Amber glass bottles with plastic screw caps of 200 ml, 300 ml and 500 ml.

HDPE bottles with plastic screw caps of 200 ml, 300 ml, 500 ml, 1000 ml and 5000 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Co-pharma
Unit 4, Metro Centre, Tolpits Lane,
Watford, Hertfordshire,
WD18 9SS United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 13606/0084

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/01/2011

10. DATE OF REVISION OF THE TEXT

16/05/2018