PRESCRIBING INFORMATION

pms-LACTULOSE

Lactulose Solution, USP

667 mg/mL

Colonic Content Acidifier - Laxative

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montreal, Quebec
H4P 2T4

www.pharmascience.com

Date of Revision:
January 21, 2015
Version 1 : September 6, 2022

Submission Control No: 180273

PRESCRIBING INFORMATION

pms-LACTULOSE
Lactulose Solution, USP

667 mg/mL

THERAPEUTIC CLASSIFICATION

Colonic Content Acidifier - Laxative

ACTION AND CLINICAL PHARMACOLOGY

pms-LACTULOSE (lactulose solution), a disaccharide sugar containing one molecule of galactose and one molecule of fructose, is a synthetic derivative of lactose. pms-LACTULOSE is a solution in water prepared from Lactulose concentrate. It contains lactulose, galactose, lactose, fructose and epilactose.

In patients with portal-systemic encephalopathy (PSE), lactulose solution causes a decrease in blood ammonia concentration and reduces the degree of PSE. Although the mechanism of action of lactulose solution has not been clearly defined, it appears to be associated primarily with the metabolism of the sugar in the lower intestinal tract. The breakdown of lactulose solution to organic acids (i.e., lactic acid and small amounts of formic and acetic acids) by the saccharolytic bacteria in the colon acidifies the contents of the colon. In patients with PSE who respond to lactulose solution, a decrease in fecal pH occurs. Acidification of colon contents inhibits the

nonionic diffusion of ammonia from the colon into the blood. In addition, since the contents of the colon are more acidic than is blood, ammonia (NH_3) can diffuse from the blood into the colon. In the acidic colon, ammonia is converted to ammonium ions ($NH4^+$) thereby preventing its absorption. In a similar manner, the absorption of amines (which may also contribute to the development of PSE) may also be reduced.

Finally the cathartic action of lactulose solution (which is probably caused by the osmotic effect of the organic acid metabolites of lactulose solution) expels the trapped ammonium ions and possibly other nitrogenous substances from the colon. The osmotic effect of the organic acid metabilites of lactulose solution causes an increase in water content of the stool and a softening of the stool; this effect on the stool may not be seen for 24-48 hours after administration of the drug. In patients with chronic constipation, the drug increases the number of bowel movements per day and the number of days when bowel movement occurs.

Following oral administration, less than 3% of a dose of lactulose solution is absorbed from the small intestine. Absorbed lactulose solution is not metabolized and is excreted in the urine unchanged within 24 hours. Unabsorbed lactulose solution reaches the colon unchanged where it is metabolized by bacteria to form lactic acid and small amounts of acetic and formic acids. The bacteria normally present in the colon that are capable of metabolizing lactulose solution include *Lactobacilli, Bacteroides, Escherichia coli*, and *Clostridia*, but not *Proteus mirabilis*, *Enterococcus faecalis* (formerly *Streptococcus faecalis*), *Salmonella*, or *Shigella*. Only negligible amounts of lactulose solution or its metabolites are absorbed from the colon.

INDICATIONS

Constipation

pms-LACTULOSE is useful as a laxative in the treatment of chronic constipation in adults and geriatric patients.

Although pms-LACTULOSE is effective in the treatment of chronic constipation, it's superiority to conventional laxative has not been established.

Portal-systemic Encephalopathy

pms-LACTULOSE is used as an adjunct to protein restriction and supportive therapy for the prevention and treatment of portal-systemic encephatopathy (PSE) including hepatic pre-coma and coma. Lactulose solution has been useful in the management of PSE resulting from surgical portacaval shunts or from chronic hepatic diseases such as cirrhosis. In patients with PSE, lactulose solution therapy reduces the blood ammonia concentration and this is usually accompanied by substantial improvement in the mental state of the patient and improved EEG tracings. Many patients are able to tolerate increased dietary protein during pms-LACTULOSE therapy.

The drug does not however alter the course of the underlying disease. Therefore, use of pms-LACTULOSE in the treatment of PSE does not obviate treatment of underlying liver disease, nor preclude other measures used in the treatment of PSE.

pms-LACTULOSE is not useful in the management of non-nitrogenous types of encephalopathy such as those induced by drugs or metabolite or electrolyte disturbances.

pms-LACTULOSE therapy is not effective in the treatment of coma associated with infectious hepatitis or other acute disorders of the liver. In a case of hyperammonemia, which was apparently caused by an inborn error of metabolism, lactulose solution therapy was ineffective.

ADVERSE EFFECTS

During the first few days of therapy, lactulose solution frequently produces gaseous distention, belching, flatulence, borborygmi, and/ or abdominal discomfort such as cramping. These adverse

effects usually subside with continued therapy, but dosage reduction may be required. Diarrhea indicates overdosage and responds to dosage reduction. Potential complications of diarrhea include fluid loss, hypokalemia, and hypernatremia. Infants receiving pms-LACTULOSE may develop dehydration and hyponatremia. Nausea and vomiting have been reported infrequently in patients receiving the drug.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
    - Fax to 1-866-678-6789 (toll-free), or
    - Mail to: Canada Vigilance Program
      Health Canada, Postal Locator 0701E
      Ottawa, ON
      K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

PRECAUTIONS AND CONTRAINDICATIONS

In the treatment of PSE, it is important to remember that the serious underlying liver disease may produce complications such as electrolyte disturbances (e.g., hypokalemia) which require additional therapy. In addition, if diarrhea occurs it may severely deplete fluids and potassium and may intensify symptoms of PSE. For these reasons, some clinicians recommend periodic determinations of serum potassium concentrations during long-term treatment with lactulose solution.

pms-LACTULOSE should be administered with caution to patients who may require electrocautery procedures during proctoscopy or colonoscopy, since the drug can cause accumulation of hydrogen gas in high concentrations, which in the presence of an electrical spark, may theoretically result in an explosive reaction. Although this reaction has not been reported to date, patients receiving pms-LACTULOSE therapy should have a thorough bowel cleansing with a nonfermentable solution prior to these procedures. In addition, insufflation of carbon dioxide may be used but is probably an unnecessary measure.

If an unusual diarrheal condition occurs during pms-LACTULOSE therapy, patients should contact their physician. Geriatric, debilitated patients who receive pms-LACTULOSE for more than 6 months should have serum electrolytes (e.g., potassium, chloride, carbon dioxide) measured periodically during therapy.

Since pms-LACTULOSE contains some free lactose and galactose, the drug should be used with caution in patients with diabetes mellitus and is contraindicated in patients who require a low-galactose diet.

Before taking this product, please tell your healthcare provider if you have any allergies to milk components, and/or any ingredient(s) listed in the product.

Pediatric Precautions

Limited information on the use of pms-LACTULOSE for prevention and treatment of PSE in young children and adolescents is available. Safety and efficacy of the drug, for the treatment of chronic constipation in children, have not been established.

Mutagenicity and Carcinogenicity

Data on the long-term mutagenic potential of lactulose solution in animals or humans and on the long-term carcinogenic potential in humans are not available. Administration of lactulose

solution in concentrations of 3% and 10% v/w in the diet of mice for 18 months did not produce evidence of carcinogenicity.

Pregnancy, Fertility. and Lactation

Use of lactulose solution during pregnancy has not been studied in humans. Reproduction studies in rats, mice, and rabbits receiving oral lactulose solution doses up to 6 times the usual human oral dose have not revealed evidence of harm to the fetus. pms-LACTULOSE should be used during pregnancy only when clearly needed.

Reproduction studies in rats, mice, and rabbits using oral lactulose solution dosages of up to 4 or 8 g/kg (6 or 12 mL/ kg) daily did not reveal evidence of impaired fertility.

It is not known if lactulose solution is distributed into milk. The drug should be used with caution in nursing women.

ACUTE TOXICITY

No information is available on the acute overdosage of lactulose solution in humans. The oral LD_{50} of the drug is 48.8 mL/kg in mice and greater than 30 mL/ kg in rats. Overdosage of lactulose solution presumably would be manifested by abdominal cramps and diarrhea (which could result in severe fluid and electrolyte depletion), and treatment would consist of fluid and electrolyte replacement, as required.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

DRUG INTERACTIONS

Laxatives

Additional laxatives should not be administered with pms-LACTULOSE, especially when pms-LACTULOSE therapy is initiated, because the loose stools produced may be falsely interpreted as an indication that adequate dosage of pms-LACTULOSE has been achieved.

Anti-infective Agents

Theoretically, orally administered neomycin and possibly other anti-infective agents, when administered concurrently with pms-LACTULOSE, could eliminate colonic bacteria that are necessary to metabolize pms-LACULOSE and thereby prevent acidification of the contents of the colon. Limited data obtained from experiments in healthy individuals tend to support the theoretical incompatibility of these agents.

Therefore, until there is conclusive evidence that concurrent administration of pms-LACTULOSE and neomycin, or other oral anti-infective agents is efficacious, patients should be closely monitored for possible inadequate responses to pms-LACTULOSE.

Antacids

Results of limited studies in rats and humans suggest that nonabsorbable antacids administered concomitantly with lactulose solution may inhibit the desired decrease in fecal pH in the colon. The potential lack of desired effect of pms-LACTULOSE should be considered before a nonabsorbable antacid is administered concomitantly with pms-LACTULOSE.

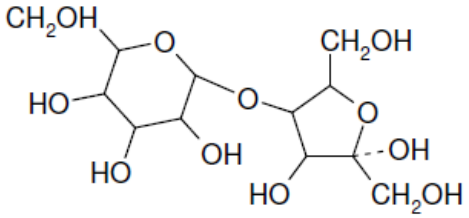
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Lactulose

Chemical Name: 4-*O*-β-D-Galactopyranosyl-D-fructofuranose

Structural Formula:



Molecular Formula : $C_{12}H_{22}O_{11}$

Molecular Weight: 342.30 g/mol

Description: Hexagonal clustered plates from methanol, mp 169°C.
Sweeter than lactose, but not as sweet as sucrose.
Solubility in water (w/w) at 30°C: 76.4%, at 60°C: 8 1 %., at 90°C: > 86%.

Storage: Store between 15°C and 30°C. Protect from freezing.

DOSAGE AND ADMINISTRATION

Administration

pms-LACTULOSE is usually administered orally. The sweet taste of pms-LACTULOSE, which may be unpleasant to some patients, can be minimized by diluting the solution with water, fruit juice, or milk, or administering it in food such as desserts. When pms-LACTULOSE is administered via a gastric tube, it should be well diluted to prevent induction of vomiting and the possibility of aspiration pneumonia.

pms-LACTULOSE may also be administered rectally to adults with portal-systemic encephalopathy (PSE), during stages of hepatic pre-coma or coma, when the possibility of aspiration exists, or when necessary endoscopic or intubation procedures interfere with oral administration.

Dosage:

Constipation:

For the treatment of chronic constipation in adults, the usual initial dosage of pms-LACTULOSE is 10 g to 20 g (15 mL to 30 mL) daily. Dosage may be increased to 40 g (60 mL) daily if necessary. Following oral pms-LACTULOSE administration, 24-48 hours may be required to restore normal bowel movements.

Portal-systemic Encephalopathy:

For the prevention and treatment of PSE in adults, the usual initial oral dosage of pms-LACTULOSE is 20 g to 30 g (30 mL to 45 mL of pms-LACTULOSE) 3 or 4 times daily. Dosage is then adjusted every 1-2 days as necessary to produce 2 or 3 soft stools daily. Some clinicians recommend that dosage be adjusted according to the acidity of the colonic contents by measuring stool pH (with indicator paper) at the start of therapy and adjusting the dosage until

stool pH is about 5. This pH is usually achieved when the patient has 2 or 3 soft stools daily during pms-LACTULOSE therapy. For most adults, pms-LACTULOSE dosage is usually 60 g to 100 g (90 mL to 150 mL) daily, although some patients may require a higher dosage.

In the management of acute episodes of PSE in adults, 20 g to 30 g (30 mL to 45 mL) may be given orally at 1 to 2 hour intervals to induce rapid laxation. When the laxative effect has been achieved, the dose of pms-LACTULOSE is reduced to the amount required to produce 2 or 3 soft stools daily. When pms-LACTULOSE is administered in the treatment of PSE, improvement in the clinical condition of the patient usually occurs within 1-3 days. Continuous long-term therapy with pms-LACTULOSE may decrease the severity and prevent the recurrence of PSE.

Based on limited information, the initial oral dosage of pms-LACTULOSE for the prevention and treatment of PSE in infants is 1.67 g to 6.67 g (2.5 mL to 10 mL) daily given in divided doses. In older children and adolescents, the total daily dose of pms-LACTULOSE is 27 g to 60 g (40 mL to 90 mL). Dosage is adjusted every 1-2 days as necessary to produce 2-3 soft stools daily. If the initial dose of pms-LACTULOSE produces diarrhea, the dose should be reduced immediately. If diarrhea persists, the drug should be discontinued.

When pms-LACTULOSE is used rectally in the treatment of PSE, to reverse hepatic coma in adults, 200 g (300 mL) is diluted with 700 mL of water or 0.9% sodium chloride solution; the diluted solution is administered rectally via a rectal balloon catheter and retained for 30-60 minutes. Lactulose retention enemas may be administered every 4-6 hours; if the enema is retained for less than 30 minutes, it may be repeated immediately. In some patients, reversal of hepatic coma may occur within 2 hours of the first enema. Before discontinuance of lactulose retention enemas, recommended oral dosages of the drug should be started. Cleansing enemas containing soapsuds or other alkaline agents should not be used concomitantly with lactulose enemas.

STORAGE

pms-LACTULOSE should be stored between 15°C and 30°C; freezing should be avoided. Although heat causes cloudiness, and heat and light cause darkening of the solutions, these changes do not indicate loss of potency. Prolonged exposure to freezing temperatures may cause pms-LACTULOSE to become semisolid and too viscous to pour; viscosity returns to normal following warming to room temperatures. pms-LACTULOSE have an expiration date of 3 years following the date of manufacture.

AVAILABILITY OF DOSAGE FORMS

Each mL of colorless to amber syrupy liquid which may exibit some precipitation and darkening upon standing, contains: lactulose 667 mg as an active ingredient and a natural orange flavor as a non-medicinal ingredient. Also contains galactose, lactose, fructose and epilactose. Available in bottle of 30 mL, and 250 mL.

MORE INFORMATION

This document plus the full Prescribing Information, prepared for health professionals, can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

Pharmascience Inc.
Montréal, Canada
H4P 2T4
www.pharmascience.com

Last revised: January 21, 2015

REFERENCES

1. Lactulose Monograph. AHFS Drug Information 2004 Monograph, American Society of Health-System Pharmacists, 2004. p. 2505-2507

2. Lactulose. Martindale (The Extra Pharmacopoeia) - Thirty-first edition, The Royal Pharmaceutical Society of Great Britain, 1996. p. 1222-1223.

3. Lactulose Monograph. CphA Monograph 2004/2005, Compendium of Pharmaceuticals and Specialties, online version (e-CPS), Canadian Pharmacists Association, 2005.