AUSTRALIAN PRODUCT INFORMATION

ACTILAX®

Lactulose oral liquid

1 NAME OF THE MEDICINE

Lactulose

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lactulose solution is an aqueous solution of lactulose (4-*O*-β-D-galacto-pyranosyl-D-fructose) and other sugars including lactose, galactose, tagatose and epilactose.

Each 5 mL contains lactulose 3.3 g, and lesser amounts of other sugars including lactose, galactose, tagatose and epilactose.

Excipients with known effect: galactose, lactose, sugars and traces of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ACTILAX oral liquid is a clear, viscous liquid, colourless or pale brownish-yellow, which is miscible with water.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. Treatment of acute, and prevention and treatment of chronic Portal-Systemic Encephalopathy (PSE), including the stages of hepatic precoma and coma.

2. Treatment of chronic and habitual constipation.

   Controlled clinical studies in patients with a history of chronic constipation have shown that lactulose therapy causes a significant increase in the number of bowel movements per day and the number of days on which bowel movements occur.

4.2 DOSE AND METHOD OF ADMINISTRATION

The lactulose solution may be administered diluted or undiluted. The dose should be titrated according to the clinical response. A single dose of lactulose should be swallowed in one and should not be kept in the mouth for an extended period of time.

Portal-Systemic Encephalopathy.

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

Dosing in PSE (for adults only): The usual dosage is 30 to 45 mL three or four times daily. The dosage may be adjusted every day or two to produce two or three soft stools daily.

Hourly doses of 30 to 45 mL of ACTILAX solution may be used to induce the rapid laxation indicated in the initial phase of the therapy of PSE. When the laxative effect has been achieved, the dose of ACTILAX may then be reduced to the recommended daily dose.

Improvement in the patient's condition may take 24 to 48 hours to occur. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of PSE. The dose of ACTILAX for this purpose is the same as the recommended daily dose.

In the treatment of acute episodes of PSE, a rapid response is desirable. In such cases it is important to avoid underdosage, and 50 mL every 1 to 2 hours can be given if necessary until two loose bowel actions have occurred. Thereafter, doses may be reduced to usual doses (30 mL four times daily).

The administration of lactulose by retention enema is an alternative technique. This can be prepared by diluting lactulose solution, and is of considerable value especially in the unconscious patient. In such cases 300 mL of ACTILAX may be mixed with 700 mL of water or normal saline to be used as a retention enema; the enema is to be retained for 30 to 60 minutes, and repeated every 4 to 6 hours until the patient is able to take oral medication.

Chronic constipation.

Dosage is individualised and depends somewhat on the severity of the constipation.

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

Adults. The usual initial dose is 15 to 30 mL daily. The dose may be increased to 45 mL daily if necessary. Since ACTILAX solution relieves constipation by producing a physiological change in the colon, it may take from 24 to 48 hours before normal defaecation occurs. After three days, the dose may be reduced to 10 to 25 mL daily for maintenance.

More serious constipation and/or constipation such as that caused by chemotherapy agents may require higher dosages.

Children. It is recommended that if ACTILAX is given to infants and children, this should be done under medical supervision. The usual initial daily doses (for the first three days) are as follows:

7 to 14 years: 15 mL

1 to 6 years: 10 mL

Infants under 1 year: 5 mL

Maintenance daily doses are as follows:

7 to 14 years: 10 mL

1 to 6 years: 5 to 10 mL

Infants under 1 year: 3 to 5 mL

Note. ACTILAX solution may be more acceptable when mixed with fruit juice, water or milk.

When experiencing constipation patients should be advised to drink plenty of water, and increase the fibre content in their diet.

4.3 CONTRAINDICATIONS

Since ACTILAX contains galactose (not more than 0.50 g/5 mL) and lactose (not more than 0.33 g/5 mL), it is contraindicated in patients who require a low galactose diet, and in patients with galactosaemia or disaccharidase deficiency or who are on a galactose and/or lactose free diet.

Contraindicated in patients with gastrointestinal obstruction, digestive perforation, or risk of digestive perforation.

Contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Painful abdominal symptoms of undetermined cause should be evaluated to exclude undiagnosed perforation or obstruction or undiagnosed disease/condition that predisposes to either before the treatment is started.

In case of insufficient therapeutic effect after several days, consultation of a physician is recommended since the dose and/or additional measures should be reconsidered.

A theoretical hazard may exist for patients treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. If sugars reach the colon and bacterial breakdown causes hydrogen production, accumulation of hydrogen gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this complication has not been reported with lactulose, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with non-fermentable solution.

ACTILAX solution contains galactose and lactose and it should be used with caution in diabetics as blood glucose levels may be elevated, usually after extended use.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

If used by lactose intolerant patients, the lactose content in the recommended dose should be taken into consideration.

Chronic misuse of laxatives may result in electrolyte imbalance, in particular serum potassium levels may be decreased. Elderly debilitated patients who receive ACTILAX solution for more than 6 months should have serum electrolytes measured periodically.

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

The defaecation reflex may be altered during the treatment with lactulose (see Section 5 PHARMACOLOGICAL PROPERTIES). This alteration is considered to improve bowel habits during constipation and can be seen as a normalization of stool frequency.

In the overall management of portal-systemic encephalopathy, it should be recognised that there is a pre-existing liver disease and efforts should be made to identify and treat the precipitating cause of hepatic coma. Thus, the overall management of hepatic encephalopathy should include dietary protein restriction, bowel cleansing and sterilisation, correction of electrolyte and fluid imbalance, provision of caloric and nutritional needs and treatment of underlying liver disease.

Use in the Elderly

No data available.

Paediatric Use

It is recommended that if ACTILAX solution is given to infants and children, this should be done under medical supervision.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Neomycin. There have been conflicting reports about the concomitant use of neomycin and lactulose solution, although in some situations, the two drugs administered together are more effective than either one alone.

Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. There have been some reports that lactulose fermenting bacteria are relatively resistant to neomycin, which might explain why a combination could work in some cases. Thus, the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral antibiotic therapy.

Other laxatives should not be used, especially during the initial phase of therapy for PSE because the loose stools resulting from their use may falsely suggest that adequate dosage has been achieved.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Lactulose solution has been shown to be effective for the treatment of constipation associated with pregnancy when administered to women at different stages of pregnancy.

Reproduction Studies: Reproduction studies with daily oral doses of lactulose solution (50% w/w) up to 12 mL/kg in mice and rats and 6 mL/kg in rabbits have not revealed any evidence of an increased occurrence of foetal damage or other deleterious effects.

Use in Lactation

There are no data on the secretion of lactulose in breast milk or the effect on the breastfed infant. Risk-benefit should be considered.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Initial dosing may produce gaseous distension with flatulence and intestinal cramps in about 20% of patients. These effects are usually mild and transient. Excessive dosage can lead to diarrhoea. If untreated potential complications of diarrhoea may include fluid loss, and electrolyte disturbances such as hypokalaemia and hypernatraemia. Less frequently, nausea, vomiting, anorexia and increased thirst have been reported.

Very rarely, infants receiving lactulose may develop dehydration and hyponatraemia.

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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data)].

	Frequency Category				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not known**
Gastrointestinal Disorders	Diarrhoea	Flatulence, abdominal pain, nausea, vomiting			
Metabolism and Nutrition Disorders					Anorexia
Investigations			Electrolyte imbalance due to diarrhoea		
General Disorders and Administration Site Conditions					Increased thirst
Immune system disorders					Hypersensitivity reactions*
Skin and subcutaneous tissue disorders					Rash*, pruritus*, urticaria*

*Post-Marketing experience

Paediatric Population:

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

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No toxicity in humans has been recorded to date. There have been no reports of accidental overdosage. In the event of acute overdosage it is expected that diarrhoea and abdominal cramps would be the major symptoms. Complications of diarrhoea may include fluid loss, and electrolyte disturbances, such as hypokalaemia and hypernatraemia, in which case treatment would consist of fluid and electrolyte replacement. Treatment would also include cessation of lactulose or dose reduction. Extensive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Therapeutic category. Laxative

A small quantity of lactulose is probably hydrolysed in the colon into its constituent monosaccharides, galactose and fructose. The end result is a change in osmotic pressure and acidification of the colonic contents resulting in an increase in stool water-content with resultant distention and softening of the stools, which in turn promotes increased peristalsis and bowel evacuation. In patients with chronic constipation, lactulose increases the number of bowel movements per day and the number of days when bowel movements occur.

Lactulose strengthens the growth of the health-promoting bacteria of the genus *Bifidobacterium* and may suppress potentially pathogenic bacteria like *Clostridium* and *Escherichia coli*. Consequently, it is often described as a prebiotic substance. Its effects on the balance of the intestinal flora may contribute to its action in hepatic encephalopathy (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Portal-Systemic Encephalopathy, below).

Metabolism In Infants

Administration of lactulose to infants fed with cow's milk produces a predominance of *lactobacilli* in the stools, thus simulating the intestinal flora following maternal milk feeding. Lactulose also appears to increase the production of lysosome in infants receiving cow's milk.

Portal-Systemic Encephalopathy (hepatic encephalopathy; "hepatic coma").

Portal-Systemic Encephalopathy (PSE) is a neuropsychiatric syndrome from a disorder of cerebral function, which can complicate all forms of liver disease. The major sites of cerebral involvement are the cortex, extra-pyramidal system and cerebellum. Clinical features include intellectual deterioration, disturbances of consciousness and neurological abnormalities.

It is generally accepted that PSE involves exposure of the brain to nitrogenous substances arising from the gut from bacterial metabolism of protein, with ammonia being implicated most commonly, together with an alteration of the pattern of amino acids entering the central nervous system.

The basic action of lactulose in PSE is aimed at reducing "nitrogenous intoxication" by decreasing blood ammonia concentration. Lactulose is degraded in the large bowel by bacterial flora, mainly to acetic and lactic acids, thus reducing the intraluminal pH to below 5. This acidification of colonic contents results in the retention of ammonia as the ammonium ion $[NH_4]^+$. In effect, ammonia, amines and various amides, and other basic nitrogenous substances are thus trapped, reducing their absorption into the blood. Since the colonic contents are more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the ammonium ion. Lowering of faecal pH is also thought to suppress urease producing organisms, and to foster the growth of saccharolytic bacteria (*Lactobacillus acidophilus*) rather than *E. coli*, a more efficient ammonia producing bacterium. The diarrhoeal action of lactulose is synergistic in expelling the trapped ammonium ion from the colon.

Thus, of several proposals, the therapeutic action of lactulose in ameliorating the symptoms of PSE is considered to be the result of the following:

1. Reduction of faecal pH leading to a reduced ammonia absorption via non-ionic diffusion and/or diffusion of ammonia from the blood into the gut. The trapped ammonia is then excreted in the stools.

2. Suppression of urease producing organisms.

3. Induction of an osmotic type of diarrhoea which diminishes faecal stasis with reduction of nitrogenous substances for ammonia production. Decreased absorption of ammonia from the gut also results from shortening intestinal transit time.

The actual mechanism may be a combination of these effects.

Clinical Trials

In the treatment of chronic portal-systemic encephalopathy, controlled studies have shown that lactulose therapy reduces the blood ammonia levels by 25 to 50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy, with the added benefit that an increase in patients' protein tolerance is frequently observed with lactulose therapy. Lactulose is an effective alternative to neomycin, particularly in patients with hearing problems or renal disease, and when long-term use is anticipated.

5.2 PHARMACOKINETIC PROPERTIES

Experimental data on lactulose given orally to man indicate that lactulose is poorly absorbed from the gastrointestinal tract and no enzymes capable of hydrolysis of lactulose into its component monosaccharides are known to be present in human gastrointestinal tissue. Lactulose reaches the colon virtually unchanged. There it is metabolised by colonic bacteria to low molecular weight acids ie. lactic acid and other short chain carboxylic acids. Metabolism is complete at doses up to 25-50 g or 40-75 mL; at higher dosages, a proportion may be excreted unchanged.

Lactulose given orally to human results in only small amounts reaching the blood by absorption through the small intestine probably by a non-mediated diffusion mechanism. Otherwise small increases in blood sugar levels are probably attributable to the small amounts of galactose and lactose also present in ACTILAX. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate or freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

500 mL oral liquid solution in a PET bottle with a PP child resistant closure.

Australian Register of Therapeutic Goods (ARTG)

AUST R 43582 – ACTILAX lactulose 660 mg/mL oral liquid bottle

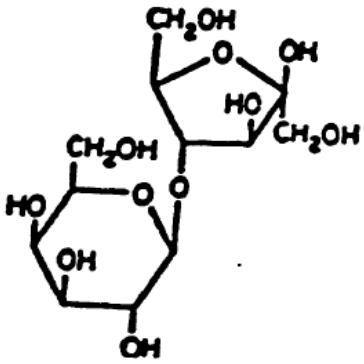
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Structural formula:



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

Mol. Wt. 342.3

CAS Number

CAS Registry no.: 4618-18-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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9 DATE OF FIRST APPROVAL

24/03/1993

10 DATE OF REVISION

10/05/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Update S1 declaration
6.5	Update container closure description

ACTILAX® is a Viatris company trade mark

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