# LACTULOSE SOLUTION- lactulose solution usp, 10 g/15 ml solution Bajaj Medical, LLC

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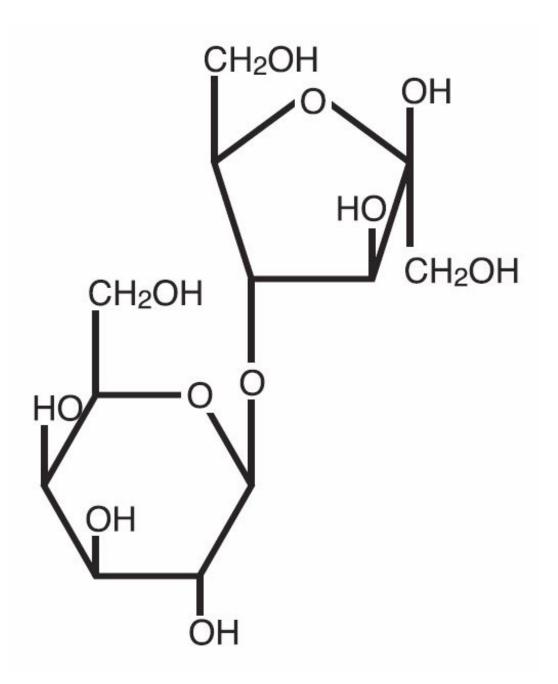
Lactulose Solution USP, 10 g/15 mL BAJAJ MEDICAL, LLC

### DESCRIPTION

Lactulose is a synthetic disaccharide in solution form for oral or rectal administration. Each 15 mL of Lactulose Solution USP contains 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). It also contains D&C Yellow No. 10, FD & C Yellow No. 6 and Purified Water.

Lactulose is a colonic acidifier for treatment and prevention of portal-systemic encephalopathy.

The chemical name for lactulose is 4-0-ß-D-galactopyranos-D-fructofuranose. It has the following structural formula:



The molecular weight is 342.30. It is freely soluble in water.

## CLINICAL PHARMACOLOGY

Lactulose causes a decrease in blood ammonia concentration and reduces the degree of portal-systemic encephalopathy. These actions are considered to be results of the following:

- Bacterial degradation of lactulose in the colon acidifies the colonic contents.
- This acidification of colonic contents results in the retention of ammonia in the colon as the ammonium ion. Since the colonic contents are then more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the ammonium ion.
- The acid colonic contents convert NH  $_3$  to the ammonium ion [NH  $_4$ ] <sup>+</sup>, trapping it and preventing its absorption.
- The laxative action of the metabolites of lactulose then expels the trapped ammonium

ion from the colon.

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

When incubated with extracts of human small intestinal mucosa, lactulose was not hydrolyzed during a 24-hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of low molecular weight acids that acidify the colon contents.

### INDICATIONS AND USAGE

For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma.

Controlled studies have shown that lactulose solution therapy reduces the blood ammonia level 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. An increase in patients' protein tolerance is also frequently observed with lactulose solution therapy. In the treatment of chronic portalsystemic encephalopathy, lactulose solution has been given for over 2 years in controlled studies.

### CONTRAINDICATIONS

Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.

### WARNINGS

A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H <sub>2</sub> 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 a non-fermentable solution. Insufflation of CO <sub>2</sub> as an additional safeguard may be pursued but is considered to be a redundant measure.

### PRECAUTIONS

**General:** Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes. In the overall management of portal-systemic encephalopathy, it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

Infants receiving lactulose may develop hyponatremia and dehydration.

### **Drug Interactions**

There have been conflicting reports about the concomitant use of neomycin and lactulose solution. 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. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy.

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

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

### Carcinogenesis, Mutagenesis, and Impairment of Fertility

There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment of fertility. There are no known animal data on long-term potential for mutagenicity. Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of carcinogenicity.

In studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

### Pregnancy: Teratogenic Effects; Pregnancy Category B.

Reproduction studies have been performed in mice, rats, and rabbits at doses up to 2 or 4 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lactulose. There are, however, no adequate and wellcontrolled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### **Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose is administered to a nursing woman.

### Pediatric Use

Very little information on the use of lactulose in pediatric patients has been recorded (see DOSAGE AND ADMINISTRATION).

### **ADVERSE REACTIONS**

Precise frequency data are not available. Lactulose may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia. Nausea and vomiting have been reported.

### OVERDOSAGE

**Signs and Symptoms:** There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated.

**Oral LD**  $_{50}$ : The acute oral LD  $_{50}$  of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

**Dialysis**: Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

### DOSAGE AND ADMINISTRATION

### Oral

**Adult:** The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily.

Hourly doses of 30 to 45 mL of lactulose may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of lactulose may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later.

Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of lactulose for this purpose is the same as the recommended daily dose.

**Pediatric:** Very little information on the use of lactulose in young children and adolescents has been recorded. As with adults, the subjective goal in proper treatment is to produce 2 to 3 soft stools daily. On the basis of information available, the recommended initial daily oral dose in infants is 2.5 to 10 mL in divided doses. For older children and adolescents, the total daily dose is 40 to 90 mL. If the initial dose causes diarrhea, the dose should be reduced immediately. If diarrhea persists, lactulose should be discontinued.

### Rectal

When the adult patient is in the impending coma or coma stage of portal-systemic encephalopathy and the danger of aspiration exists, or when the necessary endoscopic or intubation procedures physically interfere with the administration of the recommended oral doses, lactulose solution may be given as a retention enema via a rectal balloon catheter. Cleansing enemas containing soap suds or other alkaline agents should not be used.

Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic saline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be repeated immediately.

The goal of treatment is reversal of the coma stage in order that the patient may be able

to take oral medication. Reversal of coma may take place within 2 hours of the first enema in some patients. Lactulose given orally in the recommended doses, should be started before lactulose by enema is stopped entirely.

### HOW SUPPLIED

Lactulose Solution, USP, 10 g/15 mL is a clear, yellow to golden-yellow solution supplied in 1-pint (473 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 4-ounce (118 ml) amber plastic bottle and white plastic bottle with childresistant closures, 8-ounce (236 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 32-ounce (946 ml) white plastic bottle with foam-lined closure, 64-ounce (1893 ml) white plastic bottle with foam-lined closure, 15 ml and 35 ml unitdose cups.

Lactulose solution contains: 667 mg lactulose/mL (10 g/15 mL).

# Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action.

Prolonged exposure to temperatures above 86°F (30°C) or to direct light may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use.

Prolonged exposure to freezing temperatures may cause change to a semisolid, too viscous to pour. Viscosity will return to normal upon warming to room temperature.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure.

Manufactured by: Bajaj Medical, 415 W Pershing Rd., Chicago, IL 60609 USA

### LACTULOSE SOLUTION, USP 10 g/15 mL

### FOR ORAL OR RECTAL ADMINISTRATION

**INDICATION AND DOSAGE:** For the prevention and treatment of portal-systemic encephalopathy. See Prescribing Information for full details.

## EACH 15 mL (ONE UNIT DOSE OR ONE TABLESPOONFUL) CONTAINS: 10 g

lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). Also contains colors (including D&C Yellow No. 10, FD & C Yellow No. 6) and purified water. The pH range is between 2.5 and 6.5.

Some patients have found that lactulose solution may be more acceptable when mixed with fruit juice, water, or milk.

Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs.

**PHARMACIST:** Dispense in a tight, light-resistant container as defined in the USP, with child-resistant closure.

# Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

Manufactured by: Bajaj Medical

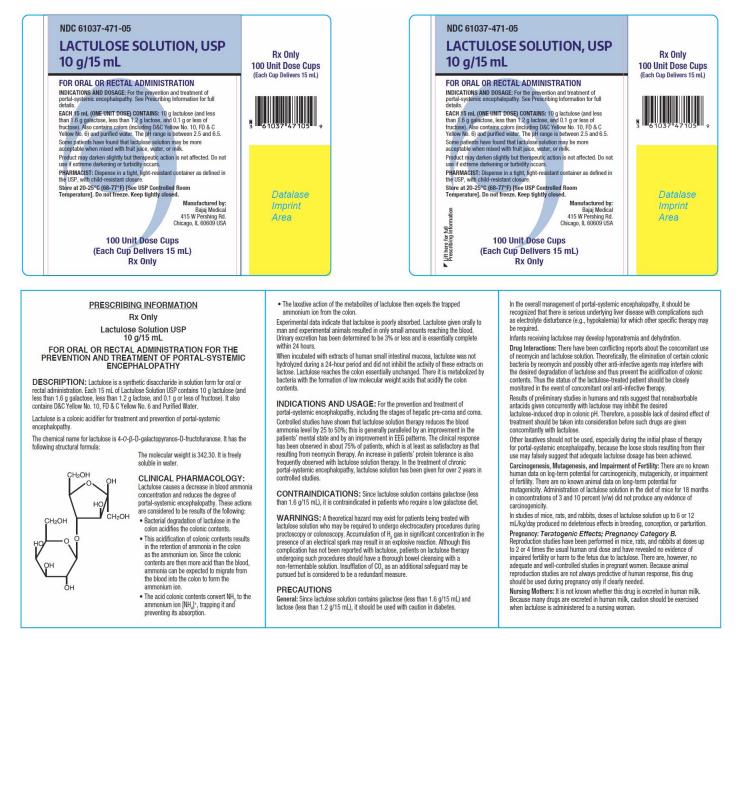
### 415 W Pershing Rd. Chicago, IL 60609 USA

### NDC 61037-471-05

### 100 Unit Dose Cups

### (Each Cup Delivers 15 mL)

### **Rx Only**



Pediatric Use: Very little information on the use of lactulose in pediatric patients has been recorded (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Precise frequency data are not available. Lactulose may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia. Nausea and vomiting have been reported.

#### OVERDOSAGE

Signs and Symptoms: There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated. Oral LD at The acute oral LD of the drug is 48.8 mL/kg in mice and greater than

30 mL/kg in rats. Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to

sucrose, however, would suggest that it should be dialyzable. DOSAGE AND ADMINISTRATION

#### Oral

Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 mL of lactulose may be used to induce the rapid laxation

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When the adult patient is in the impending coma or coma stage of portal-systemic encephalopathy and the danger of aspiration exists, or when the necessary endoscopic or intubation procedures physically interfere with the administration of the recommended oral doses, lactulose solution may be given as a retention enema via a rectal balloon catheter. Cleansing enemas containing soap suds or other alkaline agents should not be used.

Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic saline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be repeated immediately. The goal of treatment is reversal of the coma stage in order that the patient may be

able to take oral medication. Reversal of coma may take place within 2 hours of the first enema in some patients. Lactulose given orally in the recommended doses, should be started before lactulose by enema is stopped entirely.

HOW SUPPLIED: Lactulose Solution, USP, 10 g/15 mL is a clear, yellow to golden-yellow solution supplied in 1-pint (473 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 4-ounce (118 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 8-ounce (236 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 32-ounce (946 ml) white plastic and white please boute with characteristic toxices, 52-vulue (set of my white please bottle with foram-lined closure, 64-ounce (1893 ml) white plastic bottle with foam-lined closure, 15 ml and 35 ml unit-dose cups. Lactulose solution contains: 667 mg lactulose/mL (10 g/15 mL).

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 86°F (30°C) or to direct light may cause Protonged exposure to freezing temperatures above or 1(30 c) in a direct night may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use. Prolonged exposure to freezing temperatures may cause change to a semisolid, too

viscous to pour. Viscosity will return to normal upon warming to room temperature. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure.

Manufactured by: Bajaj Medical, 415 W Pershing Rd., Chicago, IL 60609 USA

### NDC 61037-471-05

### LACTULOSE SOLUTION, USP 10 g/15 mL

#### FOR ORAL OR RECTAL ADMINISTRATION

INDICATIONS AND DOSAGE: For the prevention and treatment of portal-systemic encephalopathy. See Prescribing Information for full details.

EACH 15 mL (ONE UNIT DOSE) CONTAINS: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). Also contains colors (including D&C Yellow No. 10, FD & C Yellow No. 6) and purified water. The pH range is between 2.5 and 6.5. Some patients have found that lactulose solution may be more acceptable when mixed with fruit juice, water, or milk

Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP, with child-resistant closure

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed

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Manufactured by: Bajaj Medical 415 W Pershing Rd. Chicago, IL 60609 USA

**100 Unit Dose Cups** (Each Cup Delivers 15 mL) **Rx Only** 

### NDC 61037-471-14

### **100 Cups**

### (Each Cup Delivers 30 mL)







#### PRESCRIBING INFORMATION

#### **Rx Only** Lactulose Solution USP

10 g/15 mL

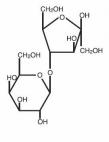
# FOR ORAL OR RECTAL ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF PORTAL-SYSTEMIC ENCEPHALOPATHY

DESCRIPTION: Lactulose is a synthetic disaccharide in solution form for oral or rectal administration. Each 15 mL of Lactulose Solution USP contains 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). It also contains D&C Yellow No. 10, PD & C Yellow No. 6 and Purified Water.

Lactulose is a colonic acidifier for treatment and prevention of portal-systemic encephalopathy

The chemical name for lactulose is 4-0-β-D-galactopyranos-D-fructofuranose. It has the following structural formula

The molecular weight is 342.30. It is freely soluble in wate



Lactulose causes a decrease in blood ammonia concentration and reduces the degree of portal-systemic encephalopathy. These actions are considered to be results of the following: • Bacterial degradation of lactulose in the colon acidifies the colonic contents.

CLINICAL PHARMACOLOGY:

- · This acidification of colonic contents results in the retention of ammonia in the color as the ammonium ion. Since the colonic contents are then more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the ammonium ion.
- . The acid colonic contents convert NH, to the ammonium ion [NH<sub>4</sub>]+, trapping it and preventing its absorption.

Pediatric Use: Very little information on the use of lactulose in pediatric patients has been recorded (see DOSAGE AND ADMINISTRATION)

ADVERSE REACTIONS: Precise frequency data are not available Lactulose may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessiv dosage can lead to diarrhea with potential complications such as loss of fluids. hypokalemia, and hypernatremia. Nausea and vomiting have been reported.

#### OVERDOSAGE

Signs and Symptoms: There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated.

Oral  $LD_{50}$ : The acute oral  $LD_{50}$  of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

#### DOSAGE AND ADMINISTRATION

#### Oral

Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. aquisite over ( ag to into in produce z or son sous sous). Hourly doese of 30 to 45 mL of lactulose may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the does of lactubes may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of lactulose for this purpose is the same as the recommended daily dose.

Pediatric: Very little information on the use of lactulose in young children and adolescents has been recorded. As with adults, the subjective goal in proper treatment is to produce 2 to 3 soft stools daily. On the basis of information available, the recommended initial daily oral dose in infants is 2.5 to 10 m. Lin divided doses. For older children and adolescents, the total daily dose is 40 to 90. mL. If the initial dose causes diarrhea, the dose should be reduced immediately. If · The laxative action of the metabolites of lactulose then expels the trapped ammonium ion from the colon.

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours

When incubated with extracts of human small intestinal mucosa, lactulose was not hydrolyzed during a 24-hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of low molecular weight acids that acidify the colon contents

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CONTRAINDICATIONS: Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.

WARNINGS: A theoretical hazard may exist for patients being treated with actulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H<sub>2</sub> gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this presence of all constrained plan may be added in all constrained readers in all constrained and a second second and the second s pursued but is considered to be a redundant measure.

#### PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes

diarrhea persists, lactulose should be discontinued. Rectal

When the adult patient is in the impending coma or coma stage of portal-systemic encephalopathy and the danger of aspiration exists, or when the necessary endoscopic or intubation procedures physically interfere with the administration of the recommended oral doses, lactulose solution may be given as a retention enema via a rectal balloon catheter. Cleansing enemas containing soap suds or other alkaline agents should not be used.

Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic aline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be repeated immediately. The goal of treatment is reversal of the coma stage in order that the patient may be

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HOW SUPPLIED: Lactulose Solution, USP, 10 g/15 mL is a clear, yellow to golden-yellow solution supplied in 1-pint (473 m) amber plastic bottle and white plastic bottle with child-resistant closures, 4-ounce (118 m) amber plastic bottle and white hastic bottle with child-resistant closures, 8-ounce (236 m) amber plastic bottle and white plastic bottle with child-resistant closures, 32-ounce (946 m)) white plastic bottle and white plastic bottle with child-resistant closures, 32-ounce (946 m)) white plastic bottle bottle with foam-lined closure, 64-ounce (1893 ml) white plastic bottle with foam-lined closure, 15 ml and 35 ml unit-dose cups. Lactulose solution contains: 667 mg lactulose/mL (10 g/15 mL).

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Manufactured by: Bajaj Medical, 415 W Pershing Rd., Chicago, IL 60609 USA

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Other laxatives should not be used, especially during the initial phase of therapy for portal-systemic encephalopathy, because the loose stools resulting from their use may falsely suggest that adequate lactulose dosage has been achieved. Carcinogenesis, Mutagenesis, and Impairment of Fertility: There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment of fertility. There are no known animal data on long-term potential for mutagenicity. Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of carcinogenicity.

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Because many drugs are excreted in human milk caution should be exercised when lactulose is administered to a nursing woman.

### NDC 61037-471-14 LACTULOSE SOLUTION, USP 10 g/15 mL

#### FOR ORAL OR RECTAL ADMINISTRATION

INDICATIONS AND DOSAGE: For the prevention and treatment of portal-systemic encephalopathy. See Prescribing Information for full details

EACH 15 mL (ONE TABLESPOONFUL) CONTAINS: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). Also contains colors (including D&C Yellow No. 10, FD & C Yellow No. 6) and purified water. The pH range is between 2.5 and 6.5. Some patients have found that lactulose solution may be more

acceptable when mixed with fruit juice, water, or milk

Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs. PHARMACIST: Dispense in a tight, light-resistant container as defined in

the USP, with child-resistant closure

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

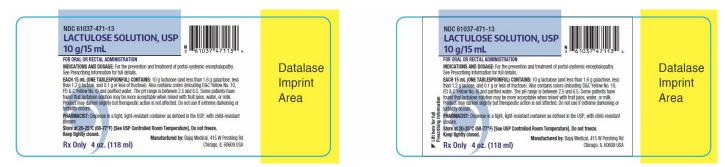
Manufactured by: Bajaj Medical 415 W Pershing Rd. Chicago. IL 60609 USA

**100 Cups** (Each Cup Delivers 30 mL) **Rx Only** 

### NDC 61037-471-13

### 4 oz. (118 ml)

### **Rx Only**



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#### PRESCRIBING INFORMATION

Rx Only

#### Lactulose Solution USP 10 g/15 mL

FOR ORAL OR RECTAL ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF PORTAL-SYSTEMIC ENCEPHALOPATHY

DESCRIPTION: Lactulose is a synthetic disaccharide in solution form for oral or rectal administration. Each 15 m. of Lactulose Solution USP contains 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose and 0.1 g or less of fructose). It also contains D&C Yellow No. 10, F0 & C Yellow No. 6 and Purtified Water.

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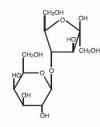
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#### PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes.

Because many drugs are excreted in human milk, caution should be exercised



The molecular weight is 342.30. It is freely soluble

**CLINICAL PHARMACOLOGY:** Lactulose causes a decrease in blood ammonia concentration and reduces the degree of portal-systemic encephalopathy. These actions are considered to be results of the following: Bacterial degradation of lactulose in the colon acidifies the colonic contents.

· This acidification of colonic contents results in In its additication of colonic contents results in the retention of ammonia in the colon as the ammonium ion. Since the colonic contents are then more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the ammonium ion. The acid antipacted proved Will to the . The acid colonic contents convert NH, to the ammonium ion [NH,]+, trapping it and preventing its absorption.

. The laxative action of the metabolites of lactulose then expels the trapped ammonium ion

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

When included with extracts of human small intestinal mucosa, lactulose was not hydrolyzed during a 24-hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of iow molecular weight acids that acidity the colon contents.

INDICATIONS AND USAGE: For the prevention and treatment of mic encephalopathy, including the stages of hepatic pre-coma and coma

Controlled studies have shown that lactulose solution therapy reduces the blood ammonia control studies have been as a second with a declared solution in reply records the block animologi level by 25 to 50%; this is generally paralleled by an improvement in the patient's 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

In the overall management of portal-systemic encentral on athy, it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required

Infants receiving lactulose may develop hyponatremia and dehydration.

Drug Interactions: There have been conflicting reports about the concomitant use of neomycin and lactulose solution. 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. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy.

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of

treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

Other laxatives should not be used, especially during the initial phase of therapy for portal-systemic encephalopathy, because the loose stools resulting from their use may falsely suggest that adequate lactulose dosage has been achieved. Carcinogenesis, Mutagenesis, and Impairment of Fertility: There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment of fertility

There are no known animal data on long-term potential for mutagenicity. Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of carcinogenicity.

In studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy: Teratogenic Effects; Pregnancy Category B. Reproduction studies have been performed in mice, rats, and rabbits at doses up to 2 or 4 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lactulose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies

are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk.

dose in infants is 2.5 to 10 mL in divided doses. For older children and adolescents, the total

daily dose is 40 to 90 mL. If the initial dose causes diarrhea, the dose should be reduced

be started before lactulose by enema is stopped entirely.

when lactulose is administered to a nursing woman. DOSAGE AND ADMINISTRATION immediately. If diarrhea persists, lactulose should be discontinued Pediatric Use: Very little information on the use of lactulose in pediatric patients has en recorded (see DOSAGE AND ADMINISTRATION). Oral Rectal Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 ml., containing 20 g to When the adult patient is in the impending coma or coma stage of portal-systemic encephalopathy and the danger of aspiration exists, or when the necessary endoscopic ADVERSE REACTIONS: Precise frequency data are not available 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to Lactulose may produce gaseous distention with flatulence or belching and abdominal or intubation procedures physically interfere with the administration of the recommended oral doses, lactulose solution may be given as a retention enema via a produce 2 or 3 soft stools daily. discomfort such as cramping in about 20% of patients. Excessive dosage can lead to Hourly doses of 30 to 45 mL of lactulose may be used to induce the rapid laxation indicated diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia. Nausea and vomiting have been reported. in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of lactulose may then be reduced to the recommended rectal balloon catheter. Cleansing enemas containing soap suds or other alkaline agents should not be used. daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic saline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to OVERDOSAGE Signs and Symptoms: There have been no reports of accidental overdosage. In the Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be event of overdosage, it is expected that diarrhea and abdominal cramps would be the repeated immediately. of portal-systemic encephalopathy. The dose of lactulose for this purpose is the same as major symptoms. Medication should be terminated. the recommended daily dose. Oral LD<sub>so</sub>: The acute oral LD<sub>so</sub> of the drug is 48.8 mL/kg in mice and greater than 30 The goal of treatment is reversal of the coma stage in order that the patient may be able to take oral medication. Reversal of coma may take place within 2 hours of the first enema in some patients. Lactulose given orally in the recommended doses, should Pediatric: Very little information on the use of lactulose in young children and adolescents has been recorded. As with adults, the subjective goal in proper treatment is to produce 2 to

3 soft stools daily. On the basis of information available, the recommended initial daily oral

sucrose, however, would suggest that it should be dialyzable.

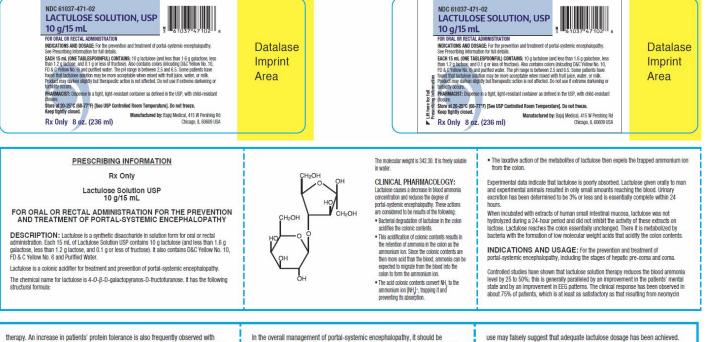
mL/kg in rats. Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to

How SUPPLED: Lachulose Solution, USP, 10 g/15 mL is a clear, yellow to golden-yellow solution supplied in 1-pint (473 m) amber plastic bottlie and while plastic bottlie with mither plastic bottlie and while plastic bottlie with mither plastic bottlie and while plastic bottlie with mither plastic bottlie with name-lined closure, 5 m and 35 m unit-does cups and 10 g on test and 35 m unit-does cups and 10 g on test an	Balaj Medical 415 W Pershing Rd. 415 W Pershing Rd. 416 Chicago, L. 60609 USA 866 867 868 868 868 868 869 869 869 869
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### NDC 61037-471-02

8 oz. (236 ml)

**Rx Only** 



lactulose solution therapy. In the treatment of chronic portal-systemic encephalopathy, lactulose solution has been given for over 2 years in controlled studies.

 $\label{eq:contraction} \begin{array}{l} \textbf{CONTRAINDICATIONS:} \ \ \ Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet. \end{array}$ 

WARNINGS: A theretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H<sub>2</sub> 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 lactuses, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with a non-fermentable solution. Insufficiation of CO, as an additional safeguard may be pursued but is considered to be a redundant measure.

#### PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes. In the overall management of portal-systemic enceptanologamy, it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

Infants receiving lactulose may develop hyponatremia and dehydration. **Drug Interactions:** There have been conflicting reports about the concomitant use of neomycin and lactulose solution. 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 additication of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy.

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

Other laxatives should not be used, especially during the initial phase of therapy for portal-systemic encephalopathy, because the loose stools resulting from their Carchiogenesis, Mutagenesis, and Impairment of Fertility: There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment of fertility.

There are no known animal data on long-term potential for mutagenicity. Administration of lactulose solution in the diel of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of carcinogenicity.

In studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturtition. **Pregnancy:** Teratogenic Effects; Pregnancy Category B. Reproduction studies have been performed in mice, rats, and rabbits at doses up to 2 or 4 times the usual human oral dose and have revealed no evidence of impaired fertility or

and obtain instant other lefts due to lactice. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised sucrose, however, would suggest that it should be dialyzable. dose in infants is 2.5 to 10 mL in divided doses. For older children and adolescents, the total when lactulose is administered to a nursing woman. daily dose is 40 to 90 mL. If the initial dose causes diarrhea, the dose should be reduced DOSAGE AND ADMINISTRATION Pediatric Use: Very little information on the use of lactulose in pediatric patients has immediately. If diarrhea persists, lactulose should be discontinued, been recorded (see DOSAGE AND ADMINISTRATION). Oral Rectal Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to When the adult patient is in the impending coma or coma stage of portal-systemic ADVERSE REACTIONS: Precise frequency data are not available 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to encephalopathy and the danger of aspiration exists, or when the necessary endoscopic Lactulose may produce gaseous distention with flatulence or belching and abdominal produce 2 or 3 soft stools daily. or intubation procedures physically interfere with the administration of the discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and Hourly doses of 30 to 45 mL of lactulose may be used to induce the rapid laxation indicated recommended oral doses. lactulose solution may be given as a retention enema via a rectal balloon catheter. Cleansing enemas containing soap suds or other alkaline in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative hypernatremia. Nausea and vomiting have been reported. agents should not be used. effect has been achieved, the dose of lactulose may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic OVERDOSAGE begin before 48 hours or even later. saline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to Signs and Symptoms: There have been no reports of accidental overdosage. In the 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated. of portal-systemic encephalopathy. The dose of lactulose for this purpose is the same as repeated immediately the recommended daily dose.  $\mbox{Oral LD}_{\rm so}$  : The acute oral  $\rm LD_{\rm so}$  of the drug is 48.8 mL/kg in mice and greater than 30 The goal of treatment is reversal of the coma stage in order that the patient may be Pediatric: Very little information on the use of lactulose in young children and adolescents able to take oral medication. Reversal of coma may take place within 2 hours of the mL/kg in rats. has been recorded. As with adults, the subjective goal in proper treatment is to produce 2 to first enema in some patients. Lactulose given orally in the recommended doses, should be started before lactulose by enema is stopped entirely. Dialvsis: Dialvsis data are not available for lactulose. Its molecular similarity to 3 soft stools daily. On the basis of information available, the recommended initial daily oral

HOW SUPPLIED: Lactulose Solution. USP. 10 g/15 mL is a clear, vellow to golden-vellow Manufactured by: NDC 61037-471-02 Not some table Labalade doublin, Ger, i by i hin La a clean, plann by getterrighten solution supplied in 1-pint (473 m) maker plastic botte and white plastic bottle with child-resistant closures, 8-ounce (184 m) amber plastic bottle and white plastic bottle with child-resistant closures, 8-ounce (946 m) white plastic bottle and white plastic bottle with child-resistant closures, 82-ounce (946 m) white plastic bottle and white plastic bottle with Bajai Medical LACTULOSE SOLUTION, USP 415 W Pershing Rd. Chicago, IL 60609 USA 10 g/15 mL 64-ounce (1893 ml) white plastic bottle with foam-lined closure, 15 ml and 35 ml unit-dose FOR OBAL OR RECTAL ADMINISTRATION INDICATIONS AND DOSAGE: For the prevention and treatment of portal-systemic encephalopathy See Prescribing Information for full details. Lactulose solution contains: 667 mg lactulose/mL (10 g/15 mL). Secretation in information for the relations. EACH 15 mL (ONE TABLESPOONFUL) CONTAINS: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructices). Also contains colors (inlouding D&C Yellow No. 10, FD & C Yellow No. 6) and purified water. The pH range is between 2.5 and 6.5. Some patients have Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed. Under recommended storage conditions, a normal darkening of color may occur. Such found that lactulose solution may be more acceptable when mixed with fruit juice, water, or milk. Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 86°F (30°C) or to direct light may cause rbidity occurs. extreme darkening and turbidity which may be pharmaceutically objectionable. If this 32 PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP, with child-resistant condition develops, do not use. Lift here for ft Prescribing In Prolonged exposure to freezing temperatures may cause change to a semisolid, too viscous to pour. Viscosity will return to normal upon warming to room temperature. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze Keep tightly closed. Manufactured by: Bajaj Medical, 415 W Pershing Rd Chicago, IL 60609 USA Rx Only 8 oz. (236 ml) closure. .

### NDC 61037-471-12

16 fl oz (473 mL)

### **Rx Only**



PRESCRIBING INFORMATION Rx Only Lactulose Solution USP 10 g/15 mL

#### FOR ORAL OR RECTAL ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF PORTAL-SYSTEMIC ENCEPHALOPATHY

DESCRIPTION: Lactulose is a synthetic disaccharide in solution form for oral or rectal administration. Each 15 mL of Lactulose Solution USP contains 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). It also contains D&C Yallow No. 10, FD & C Yellow No. 6 and Purtified Water.

Lactulose is a colonic acidifier for treatment and prevention of portal-systemic encephalopathy.

OH

CH<sub>2</sub>OH

HO

CH<sub>2</sub>OH

CH2OH

The chemical name for lactulose is 4-0-β-D-galactopyranos-D-fructofuranose. It has the following structural formula:

The molecular weight is 342.30. It is freely soluble in water.

CLINICAL PHARMACOLOGY: Lactulose causes a decrease in blood ammonia concentration and reduces the degree of portal-systemic encephalopathy. These actions are considered to be results of the following: • Bacterial degradation of factulose in the

- colon acidifies the colonic contents. • This acidification of colonic contents results in the retention of ammonia in the colon as the ammonium ion. Since the colonic contents are then more acid than the blood,
- ammonia can be expected to migrate from the blood into the colon to form the ammonium ion. The acid colonic contents convert NH, to th
- The acid colonic contents convert NH, to the ammonium ion [NH,]\*, trapping it and preventing its absorption.

The laxative action of the metabolites of lactulose then expels the trapped
 ammonium ion from the colon.

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

When incubated with extracts of human small intestinal mucosa, lactulose was not hydrolyzed during a 24-hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of low molecular weight acids that acidify the colon contents.

INDICATIONS AND USAGE: For the prevention and treatment of portal-systemic enceptaliopathy, including the stages of hegetic pre-coma and coma. Controlled studies have shown that lactuices solution therapy reduces the blood ammonia level by 25 to 50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EGS patterns. The colinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neornyoin therapy. An increase in patients' protein loierance is also trequently observed with lactuices solution therapy. In the treatment of chronic opral-systemic encephalopathy, lactulose solution has been given for over 2 years in controlled studies.

 $\label{eq:contraction} \textbf{CONTRAINDICATIONS:} Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.$ 

WARNINGS: A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H, 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 a non-fermentable solution. Insuffication (20, as an additional safeguard may be pursued but is considered to be a redundant measure.

#### PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes. In the overall management of portal-systemic encephalopathy, it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

Infants receiving lactulose may develop hyponatremia and dehydration. Drug Interactions: There have been conflicting reports about the concomitant use of neomycin and lactulose solution. 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. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy. Beauth of certainingen charlies in thumane and the suggest the popercentable

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-Induced drop in colonic pit. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility: There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment of fertility. There are no known aminal data on long-term potential for mutagenicity. Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (viw) did not produce any evidence of carcinogenicity.

In studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy: Teratogenic Effects; Pregnancy Category B. Reproduction studies have been performed in mice, rats, and rabbits at doese up to 2 or 4 times the usual human oral does and have revealed no evidence of impaired fertility or harm to the fetus due to lactudes. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose is administered to a nursing woman. Pediatric Use: Very little information on the use of lactulose in pediatric patients has been recorded (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Precise frequency data are not available Lactulose may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypematremia. Nausea and vomiting have been reported.

#### OVERDOSAGE

Signs and Symptoms: There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated. Oral LD  $_{\rm so}$ : The acute oral LD  $_{\rm so}$  of the drug is 48.8 mL/kg in mice and greater than

30 mL/kg in rats. Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

#### DOSAGE AND ADMINISTRATION

#### Oral

Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily.

Houry doese of 30 to 45 mL of lactulose may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of lactulose may then be Think the addance on the recommended daily does. Improvement in the patients condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The does of lactulose for this purpose is the same as the recommended daily dose.

Pediatric: Very little information on the use of lactulose in young children and adolescents has been recorded. As with adults, the subjective goal in proper mi. If the initial dose causes diarrhea, the dose should be reduced immediately. If diarrhea persists, lactulose should be discontinued. Rectal

When the adult patient is in the impending coma or coma stage of portal-systemic encephalopathy and the danger of aspiration exists, or when the necessary endoscopic or incluation procedures physically interfere with the administration of the recommended oral doses, lactulose solution may be given as a retention enema via a rectal balloon catheter. Cleansing enemas containing soap suds or other alkaline agents should not be used.

Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic saline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may b repeated immediately.

The goal of treatment is reversal of the coma stage in order that the patient may be Table to take orall medication. Reversal of coma may take place within 2 hours of the first enema in some patients. Lactulose given orally in the recommended doses, sho be started before lactulose by enema is stopped entirely. nded doses, should

HOW SUPPLIED: Lactulose Solution, USP, 10 g/15 mL is a clear, vellow to polen yellow solution supplied in 1-pint (473 m) amber plastic bottle and white plastic bottle with child-resistant closures, 4-ounce (118 m) amber plastic bottle and white white plastic bottle with child-resistant closures, 8-ounce (236 m) amber plastic bottle and white plastic bottle with child-resistant closures, 8-ounce (236 m) amber plastic bottle and white plastic bottle with child-resistant closures, 32-ounce (946 ml) white plastic and white plastic bother with characteristic closures, ac-ounce (see thin) white plastic bother with foram-lined closure, 64-ounce (1893 ml) white plastic bother with foam-lined closure, 15 ml and 35 ml unit-dose cups. Lactulose solution contains: 667 mg lactulose/mL (10 g/15 mL).

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze, Keep tightly closed.

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. and the prolonged exposure to temperatures above 86°F (30°C) or to direct light may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use.

Prolonged exposure to freezing temperatures may cause change to a semisolid, too viscous to pour. Viscosity will return to normal upon warming to room temperature. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure.

Manufactured by: Bajaj Medical, 415 W Pershing Rd., Chicago, IL 60609 USA

### NDC 61037-471-12 LACTULOSE SOLUTION, USP 10 g/15 mL

#### FOR ORAL OR RECTAL ADMINISTRATION

INDICATIONS AND DOSAGE: For the prevention and treatment of portal-systemic encephalopathy. See Prescribing Information for full details.

EACH 16 mL (ONE TABLESPOONFUL) CONTAINS: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). Also contains colors (including D&C Yellow No. 10, FD & C Yellow No. 6) and purified water. The pH range is between 2.5 and 6.5. Some patients have found that lactulose solution may be more

acceptable when mixed with fruit juice, water, or milk.

Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP, with child-resistant closure

**Rx Only** 

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

Manufactured by: Bajaj Medical 415 W Pershing Rd. Chicago, IL 60609 USA

nation Infor Lift here for f Prescribing Ir 16 fl oz (473 mL)

### NDC 61037-471-03

### 32 fl oz (946 mL)







#### PRESCRIBING INFORMATION

Rx Only Lactulose Solution USP

#### 10 g/15 mL

FOR ORAL OR RECTAL ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF PORTAL-SYSTEMIC ENCEPHALOPATHY

DESCRIPTION: Lactulose is a synthetic disaccharide in solution form for oral or rectal administration. Each 15 mL of Lactulose Solution USP contains 10 g lachulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). It also contains D&C vellow No. 10, FD & C Vellow No. 6 and Purified Water.

Lactulose is a colonic acidifier for treatment and prevention of portal-systemic encephalopathy.

The chemical name for lactulose is 4-0-β-D-galactopyranos-D-fructofuranose. It has the following structural formula:

The molecular weight is 342.30. It is freely soluble in water.

CH2OH OH OH

CLINICAL PHARMACOLOGY: Lactulose causes a decrease in blood ammonia concentration and reduces the degree of portal-systemic encephalopathy. These actions are considered to be results of the following: • Bacterial degradation of lactulose in the

colon acidifies the colonic contents.

- This acidification of colonic contents results in the retention of ammonia in the colon as the ammonium ion. Since the colonic contents are then more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the ammonium ion.
- The acid colonic contents convert NH, to the ammonium ion [NH,]+, trapping it and preventing its absorption.

Pediatric Use: Very little information on the use of lactulose in pediatric patients has been recorded (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Precise frequency data are not available. Lactulose may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarthea with potential complications such as loss of fluids, hypokalemia, and hypernatremia. Nausea and vomiting have been reported.

#### OVERDOSAGE

Signs and Symptoms: There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated.

 $\textbf{Oral LD}_{so}\text{-}$  The acute oral LD $_{so}$  of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

#### DOSAGE AND ADMINISTRATION

#### Oral

Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to 30 g of factulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily. Hourly doses of 30 to 45 mL of factulose may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of factulose may then be reduced to the recommended daily dose. Inprovement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrect of portal-systemic encephalopathy. The dose of factulose for this purpose is the same as the recommended daily dose.

Pediatric: Very little information on the use of lactulose in young children and adolescents has been recorded. As with adults, the subjective goal in proper treatment is to produce 2 to 3 soft solok daily. On the basis of information available, the recommended initial daily oral dose in infants is 2.5 to 10 mL in divided doses. For older children and adolescents, the total daily dose is 40 to 90 mL. If the initial dose causes dairnea, the dose should be reduced immediately. It  The laxative action of the metabolites of lactulose then expels the trapped ammonium ion from the colon.

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimental animats resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

When incutated with extracts of human small intestinal mucosa, lactulose was not hydrolyzed during a 24-hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of low molecular weight acids that acidity the colon contents.

INDICATIONS AND USAGE: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hegatic pre-coma and coma. Controlled studies have shown that lactulose solution therapy reduces the blood ammonia level by 25 to 50%; this 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. An increase in patients' protein tolerance is also frequently observed with lactulose solution therapy. In the treatment of chronic portal-systemic encephalopathy, lactulose solution has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.

WARMINGS: A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H, 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, relatents on lactiouse therapy undergoing such procedures should have a thorough bowel deansing with a non-fermentable solution. Insufficient on CO<sub>2</sub> as an additional safeguard may be pursued but is considered to be a redundant measure.

#### PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes.

diarrhea persists, lactulose should be discontinued. Rectal

When the adult patient is in the impending coma or coma stage of portal-systemic encephalopathy and the danger of aspiration exists, or when the necessary endoscopic or inhubation productures physically interfere with the administration of the recommended oral doese, lactulose solution may be given as a retention enema via a rectal balloon catheter. Cleansing enemas containing scap suds or other alkaline agents should not be used.

Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic saline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be receated immediately.

The goal of treatment is reversal of the coma stage in order that the patient may be able to take oral medication. Reversal of coma may take place within 2 hours of the first enema in some patients. Lactulose given orally in the recommended doses, should be startice Uefore lactulose by enema is stopped entrely.

HOW SUPPLIED: Lactulose Solution, USP, 10 g/15 mL is a clear, yellow to golden-yellow solution supplied in 1-pint (473 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 4-ounce (18 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 8-ounce (36 ml) amber plastic bottle and white plastic bottle with child-resistant closures, 32-ounce (946 ml) white plastic bottle with foam-lined closure, 64-ounce (1893 ml) white plastic bottle with foam-lined closure, 15 ml and 35 ml unit-dose cups.

Lactulose solution contains: 667 mg lactulose/mL (10 g/15 mL). Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 86°° (20°C) or to direct light may cause externe darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use.

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In the overall management of portal-systemic encephalopathy, it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

Infants receiving lactulose may develop hyponatremia and dehydration. **Drug Interactions:** There have been conflicting reports about the concomitant use of neomycin and lactulose solution. 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. Thus he status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy.

Results of preliminary studies in humans and rats suggest that nonabsorbable antackis given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

Other laxatives should not be used, especially during the initial phase of therapy for portial-systemic encephalopathy, because the loose stools resulting from their use may failey suggest that adequate lactudose dosage has been achieved. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment of fertility. There are no known minimal data on long-term potential for mutagenicity. Administration of factulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of carcinogenicity.

In studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy: Teratogenic Effects; Pregnancy Category B. Reproduction studies have been performed in mice, rats, and rabitis at doses up to 2 or 4 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lacticulose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose is administered to a nursing woman.

### NDC 61037-471-03 LACTULOSE SOLUTION, USP 10 g/15 mL

#### FOR ORAL OR RECTAL ADMINISTRATION

INDICATIONS AND DOSAGE: For the prevention and treatment of portal-systemic encephalopathy. See Prescribing Information for full details.

EACH 15 mL (ONE TABLESPOONFUL) CONTAINS: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). Also contains colors (including D&C Yellow No. 10, FD & C Yellow No. 6) and purified water. The H range is between 2.5 and 6.5. Some patients have found that lactulose solution may be more

acceptable when mixed with fruit juice, water, or milk.

Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP, with child-resistant closure. Store at 20-25°C (68-77°F) [See USP Controlled Room

Temperature]. Do not freeze. Keep tightly closed.

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32 fl oz (946 mL) Rx Only

NDC 61037-471-04

64 fl oz (1893 mL)

**Rx Only** 



#### PRESCRIBING INFORMATION Rx Only

Lactulose Solution USP

10 g/15 mL FOR ORAL OR RECTAL ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF PORTAL-SYSTEMIC ENCEPHALOPATHY

DESCRIPTION: Lactulose is a synthetic disaccharide in solution form for oral or rectal administration. Each 15 mL of Lactulose Solution USP contains 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). It also contains D&C Yellow No. 10, FD & C Yellow No. 6 and Purtiled Water.

Lactulose is a colonic acidifier for treatment and prevention of portal-systemic encephalopathy.

The chemical name for lactulose is 4-0-β-D-galactopyranos-D-fructofuranose. It has the following structural formula:

The molecular weight is 342.30. It is freely soluble in water.

#### CLINICAL PHARMACOLOGY: Lactulose causes a decrease in blood ammonia concentration and reduces the degree of

concentration and reduces the degree of portal-systemic encephalopathy. These actions are considered to be results of the following: • Bacterial degradation of lactulose in the

- colon acidifies the colonic contents. • This acidification of colonic contents results in the retention of ammonia in the colon contents are then more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the
- ammonium ion. • The acid colonic contents convert NH, to the ammonium ion [NH,]+, trapping it and preventing its absorption.

The laxative action of the metabolites of lactulose then expels the trapped
ammonium ion from the colon.

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimential animals resulted in only small amounts reaching the blood. Urinary excertein has been determined to be 3% or less and is essentially complete within 24 hours.

When incubated with extracts of human small intestinal mucosa, lactulose was not hydrolyzed during a 24-hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of low molecular weight acids that acidify the colon contents.

INDICATIONS AND USAGE: For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma.

Controlled studies have shown that lactulose solution therapy reduces the blood ammonia level by 25 to 50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patients. The cellicial response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose solution therapy. In the treatment of chronic opratal-systemic encephalopathy, lactulose solution has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.

WARNINGS: A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumutation of H<sub>2</sub> 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 a non-fermentable solution. Insufficiant of CO, as an additional safeguard may be purved but is considered to be a redundant measure.

#### PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes.

Pediatric Use: Very little information on the use of lactulose in pediatric patients has been recorded (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Precise frequency data are not available. Lactulose may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage can lead to diarthea with potential complications such as loss of fluids, hypokalemia, and hypernatremia. Nausea and vomiting have been reported.

#### OVERDOSAGE

Signs and Symptoms: There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated.

Oral LD<sub>60</sub>: The acute oral LD<sub>50</sub> of the drug is 48.8 mL/kg in mice and greater than 30 mL/kg in rats.

Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

#### DOSAGE AND ADMINISTRATION

#### Oral

Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily.

Houry losses of 30 to 45 m<sup>2</sup>, of lachulose may be used to induce the rapid laxation indicated in the initial phase of the thrapy of portal-systemic encephalopathy, When the laxative effect has been achieved, the dose of lachulose may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of lachulose for this purpose is the same as the recommended daily dose.

Peopletric: very little information on the use of lactulose in young children and adolescents has been recorded. As with adults, the subjective goal in proper treatment is to produce 2 to 3 soft stools daily. On the basis of information available, the recommended initial daily oral does in infants is 2.5 to 10 mL in divided doses. For older children and adolescents, the total daily dose is 40 to 90 mL. If the initial dose causes diamhea, the dose should be reduced immediately. It diarrhea persists, lactulose should be discontinued. Rectal

When the adult patient is in the impending coma or coma stage of portal-systemic encephalogathy and the danger of aspiration exists, or when the necessary endoscopic or inhubation productures physically interfere with the administration of the recommended oral doses, lactulose solution may be given as a retention enema via a rectal balioon catheter. Cleansing enemas containing scap suds or other alkaline agents should not be used.

Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic saline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be repeated immediately.

The goal of treatment is reversal of the coma stage in order that the patient may be able to take oral medication. Reversal of coma may take place within 2 hours of the first enmain is some patients. Lacklose given orally in the recommended doses, should be started before lackulose by enema is stopped entirely.

HOW SUPPLIED: Lactudose Solution, USP, 10 g/15 mL is a clear, yellow to golden-yellow solution supplied in 1-pint (473 m) amber plastic bottle and white plastic bottle with childr-resistant closures, 4-ounce (136 m) amber plastic bottle with white plastic bottle with childr-resistant closures, 8-ounce (236 m) amber plastic bottle and white plastic bottle with childr-resistant closures, 3-ounce (436 m) amber plastic bottle bottle with foam-lined dosure, 64-ounce (1893 m)) white plastic bottle with foam-lined closure, 15 ml and 35 ml unit-dose cups. Lactudose solution contains: 667 mg lactudose/mL (10 g/15 mL).

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 86°F (30°C) or to direct light may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use.

externer dankening and undruk y which may be priamaceducany objectionalie. It un condition develops, do not use. Prolonged exposure to freezing temperatures may cause change to a semisolid, too viscous to pour. Viscosity will return to normal upon warming to room temperature. Dispense in a tiptic, light-resistant container as defined in the USP, with a child-resistant closure.

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### NDC 61037-471-04 LACTULOSE SOLUTION, USP 10 g/15 mL

In the overall management of portal-systemic encephalopathy, it should be

Infants receiving lactulose may develop hyponatremia and dehydration.

be required.

carcinogenicity.

recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may

Drug Interactions: There have been conflicting reports about the concomitant use of neomycin and lactulose solution. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with

backets by horing that possibly contrain the provide the function of the function of the interface of the degradation of factulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy.

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of

Carcinogenesis, Mutagenesis, and Impairment of Fertility: There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment

Infinite reads on operating potential or each registration, indeal potential or impermented of fertility. There are no known animal data on long-term potential for mutagenicity. Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (v/w) did not produce any evidence of the evidence mitting of the solution.

In studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12

Pregnancy: Teratogenic Effects; Pregnancy Category B.

should be used during pregnancy only if clearly needed.

mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Reproduction studies have been performed in mice, rats, and rabbits at doses up to 2 or 4 times the usual human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to lactulose. There are, however, no

adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose is administered to a nursing woman.

lacebook induced copy incoloure primitively a pocean water or balance true treatment should be taken into consideration before such drugs are given concomitantly with lactulose. Other laxatives should not be used, especially during the initial phase of therapy for portal-systemic encephalopathy, because the lose shols resulting from theil use may faisely suggest that adequate lactulose dosage has been achieved.

#### FOR ORAL OR RECTAL ADMINISTRATION

INDICATIONS AND DOSAGE: For the prevention and treatment of portal-systemic encephalopathy. See Prescribing Information for full details.

EACH 15 mL (ONE TABLESPOONFUL) CONTAINS: 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). Also contains colors (including D&C Yellow No. 10, FD & C Yellow No. 6) and purified water. The pH range is between 2.5 and 6.5. Some patients have found that lactulose solution may be more

acceptable when mixed with fruit juice, water, or milk.

Product may darken slightly but therapeutic action is not affected. Do not use if extreme darkening or turbidity occurs. PHARMACIST: Dispense in a tight, light-resistant container as defined in

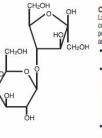
the USP, with child-resistant closure.

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

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64 fl oz (1893 mL) Rx Only



### NDC 61037-471-06

### 128 fl oz (3785 mL)

### **Rx Only**



PRESCRIBING INFORMATION Rx Only

Lactulose Solution USP 10 g/15 mL

FOR ORAL OR RECTAL ADMINISTRATION FOR THE PREVENTION AND TREATMENT OF PORTAL-SYSTEMIC ENCEPHALOPATHY

DESCRIPTION: Lactulose is a synthetic disaccharide in solution form for oral or rectal administration. Each 15 mL of Lactulose Solution USP contains 10 g lactulose (and less than 1.6 g galactose, less than 1.2 g lactose, and 0.1 g or less of fructose). It also contains D&C Yellow No. 10, FD & C Yellow No. 6 and Purtfied Water.

Lactulose is a colonic acidifier for treatment and prevention of portal-systemic encephalopathy.

OH

CH2OH

но

CH<sub>2</sub>OH

CH<sub>2</sub>OH

The chemical name for lactulose is 4-0-β-D-galactopyranos-D-fructofuranose. It has the following structural formula:

The molecular weight is 342.30. It is freely soluble in water.

CLINICAL PHARMACOLOGY: Lactulose causes a decrease in blood ammonia concentration and reduces the degree of portal-systemic encephalopathy. These actions are considered to be results of the following: • Bacterial degradation of lactulose in the

colon acidifies the colonic contents. • This acidification of colonic contents results in the retention of ammonia in the colon as the ammonium ion. Since the colonic contents are then more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the

ammonium ion. • The acid colonic contents convert NH, to the ammonium ion [NH,]+, trapping it and preventing its absorption.  The laxative action of the metabolites of lactulose then expels the trapped ammonium ion from the colon.

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

When incutatel with extracts of human small intestinal mussas, lactulose was not hydrolyzed during a 24-hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of low molecular weight acids that acidity the colon contents.

INDICATIONS AND USAGE: For the prevention and treatment of portal-systemic encephalopathy, lincluding the stages of hepatic pre-coma and coma. Controlled studies have shown that lactuices solution threapy reduces the blood ammonia level by 25 to 50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The editical response these been observed in about 75% of patients, which is at least as satisfactory as that resulting from neornycin therapy. An increase in patients' protein tolerance is also frequently observed with lactubes solution therapy. In the treatment of chronic portal-systemic encephalopathy, lactubes solution has been given for over 2 years in controlled studies.

CONTRAINDICATIONS: Since lactulose solution contains galactose (less than 1.6 g/15 mL), it is contraindicated in patients who require a low galactose diet.

WARNINGS: A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accuruatianto of H, 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 a non-fermentable solution. Insufficient of CO, as an additional safeguard may be pursued but is considered to be a redundant measure.

#### PRECAUTIONS

General: Since lactulose solution contains galactose (less than 1.6 g/15 mL) and lactose (less than 1.2 g/15 mL), it should be used with caution in diabetes. In the overall management of portal-systemic encephalopathy, it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (e.g., hypokalemia) for which other specific therapy may be required.

Infants receiving lactulose may develop hyponatremia and dehydration. **Drug Interactions:** There have been conflicting reports about the concomitant use of neomycin and lactulose solution. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactuloses and thus prevent the actidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy.

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with lactulose.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility: There are no known human data on log-term potential for carcinogenicity, mutagenicity, or impairment of fertility. There are no known animal data on long-term potential for mutagenicity. Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10 percent (viw) did not produce any evidence of carcinogenicity.

In studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 mL/kg/day produced no deleterious effects in breeding, conception, or parturition.

Pregnancy: Teratogenic Effects; Pregnancy Category B. Reproduction studies have been performed in mice, rats, and rabbits at doses up to 2 or 4 times the usual human oral dose and have revealed no evidence of impaired feitility or harm to the fetus due to lactudose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during noreancev on will clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lactulose is administered to a nursing woman.

Pediatric Use: Very little information on the use of lactulose in pediatric patients has been recorded (see DOSAGE AND ADMINISTRATION)

ADVERSE REACTIONS: Precise frequency data are not available. Lactulose may produce gaseous distention with flatulence or belching and addominal discontrof such as cramping in about 20% of patients. Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia. Nausea and vomiting have been reported.

#### OVERDOSAGE

Signs and Symptoms: There have been no reports of accidental overdosage. In the event of overdosage, it is expected that diarrhea and abdominal cramps would be the major symptoms. Medication should be terminated. Oral LD,...: The acute oral LD,... of the drug is 48.8 mL/kg in mice and greater than

30 mL/kg in rats Dialysis: Dialysis data are not available for lactulose. Its molecular similarity to sucrose, however, would suggest that it should be dialyzable.

#### DOSAGE AND ADMINISTRATION Oral

Adult: The usual adult oral dosage is 2 to 3 tablespoonfuls (30 to 45 mL, containing 20 g to 30 g of lactulose) three or four times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily.

Houry doese of 30 to 45 mL of lactulose may be used to induce the rapid faxation indicated in the initial place of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the does of lactulose may then be reduced to the recommended daily does. Improvement in the patient's condition Todace to the recommode dairy dock important in the patient's common may occur within 2 hours but may not begin before 48 hours or even later. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encorphilophilty. The does of lactulose for this purpose is the same as the recommended daily dose.

Pediatric: Very little information on the use of lactulose in young children and adolescents has been recorded. As with adults, the subjective goal in proper treatment is to produce 2 to 3 soft stools daily. On the basis of information available, the recommended initial daily or all dose in infants is 2.5 to 10 mL in divided doses. For older children and adolescents, the total daily dose is 40 to 90 mL. If the initial dose causes diarrhea, the dose should be reduced immediately. If

diarrhea persists, lactulose should be discontinued. Rectal

When the adult patient is in the impending coma or coma stage of portal-systemic recommended oral doses, lactulose solution may be given as a retention energy lacture. rectal balloon catheter. Cleansing enemas containing soap suds or other alkaline agents should not be used.

Three hundred mL of lactulose should be mixed with 700 mL of water or physiologic aline and retained for 30 to 60 minutes. Lactulose enema may be repeated every 4 to 6 hours. If this lactulose enema is inadvertently evacuated too promptly, it may be repeated immediately.

The goal of treatment is reversal of the coma stage in order that the patient may be The goal of occurrence of the first enema in some patients. Lactulose given orally in the recommended doses, should be started before lactulose by enema is stopped entirely.

HOW SUPPLIED: Lactulose Solution, USP, 10 g/15 mL is a clear, vellow to polen-yellow solution supplied in 1-pint (473 m) amber plastic bottle and white plastic bottle with child-resistant closures, 4-ounce (118 m) amber plastic bottle and white plastic bottle with child-resistant closures, 8-ounce (236 m) amber plastic bottle and white plastic bottle with child-resistant closures, 32-ounce (946 ml) white plastic and wine plastic bottle with frame-testatin closures, se-voluce (set of in) white plastic bottle with foam-lined closure, 64-vonce (1893 ml) white plastic bottle with foam-lined closure, 15 ml and 35 ml unit-dose cups. Lactulose solution contains: 667 mg lactulose/mL (10 g/15 mL).

Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Do not freeze. Keep tightly closed.

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 86°F (30°C) or to direct light may cause Protocol exposure to temporatures above or 100 of the direct right may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use. Prolonged exposure to freezing temperatures may cause change to a semisolid, too

viscous to pour. Viscosity will return to normal upon warming to room temperature. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure

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### NDC 61037-471-06 LACTULOSE SOLUTION, USP

10 g/15 mL

Free 



128 fl oz (3785 mL) **Rx Only** 

### LACTULOSE SOLUTION

lactulose solution usp, 10 g/15 ml solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:61037-471
Route of Administration	ORAL, RECTAL		

Active Ingredient/Active Moiety			
	Ingredient Name	<b>Basis of Strength</b>	Strength
	LACTULOSE (UNII: 9U7D5QH5AE) (LACTULOSE - UNII:9U7D5QH5AE)	LACTULOSE	10 g in 15 mL

Inchive	Ingredients
Inactive	marealents

Ingredient Name Stren		
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)		
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)		
WATER (UNII: 059QF0KO0R)		

### **Product Characteristics**

Color	yellow (Yellow to Golden Yellow)	Score
Shape		Size
Flavor		Imprint Code
Contains		

Packaging

#	Item Code	Code Package Description Date		Marketing End Date
1	NDC:61037- 471-05	15 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product	10/14/2021	
2	NDC:61037- 471-14	30 mL in 1 CUP, UNIT-DOSE; Type 0: Not a Combination Product	10/14/2021	
3	NDC:61037- 471-13	118 mL in 1 BOTTLE; Type 0: Not a Combination Product	10/14/2021	
4	NDC:61037- 471-02	236 mL in 1 BOTTLE; Type 0: Not a Combination Product 10/14/2021		
5	NDC:61037- 471-12	473 mL in 1 BOTTLE; Type 0: Not a Combination Product	10/14/2021	
6	NDC:61037- 471-03	946 mL in 1 BOTTLE; Type 0: Not a Combination Product	10/14/2021	
7	NDC:61037- 471-04	1893 mL in 1 JUG; Type 0: Not a Combination Product	10/14/2021	
8	NDC:61037- 471-06 3785 mL in 1 JUG; Type 0: Not a Combination Product		10/14/2021	
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
		ANDA076645	10/14/2021	

# Labeler - Bajaj Medical, LLC (078774921)

## Registrant - Bajaj Medical, LLC (078774921)

Establishment			
Name	Address	ID/FEI	Business Operations
Bajaj Medical, LLC		078774921	analysis(61037-471) , label(61037-471) , manufacture(61037-471) , pack(61037-471)

Revised: 12/2022

Bajaj Medical, LLC