

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions

## **1. NAME OF THE MEDICINAL PRODUCT**

LacTEST 0.45 g powder for oral solution

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One sachet contains 0.45 g of gaxilose.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

White or almost white powder for oral solution.

## **4. CLINICAL PARTICULARS**

### **4.1. Therapeutic indications**

This medicinal product is for diagnostic use only.

LacTEST is indicated for the diagnosis of hypolactasia in adults and elderly patients presenting with clinical symptoms of lactose intolerance.

### **4.2. Posology and method of administration**

This medicinal product should be prescribed by a gastroenterologist and must only be administered by duly authorized healthcare professionals under suitable medical supervision.

#### Posology

In adults, 0.45 g of gaxilose by oral administration.

#### *Elderly population*

The use of LacTEST is not recommended in elderly with abnormal renal function (proven by previous measurement of glomerular filtration rate  $GFR < 90 \text{ ml/ min/1.73m}^2$ ), since renal excretion of xylose may be reduced and the safety and efficacy of LacTEST have not been established.

#### *Paediatric population*

The safety and efficacy of LacTEST in children aged 0 to 18 years have not been established.

No data are available.

#### *Patients with renal impairment*

The safety and efficacy of LacTEST in patients with renal impairment have not been established. In patients with serious kidney disease, the use of LacTEST is contraindicated (see section 4.3.).

### *Patients with hepatic impairment*

The safety and efficacy of LacTEST in patients with hepatic impairment have not been established. In patients with portal hypertension (ascites, cirrhosis), the use of LacTEST is contraindicated (see section 4.3.).

### Method of administration

#### *Precautions to be taken before handling or administering LacTEST*

After reconstitution of the product by dissolving in water, a clear and colourless solution will be obtained.

The performance of the test will have the following sequence: the patient will empty his/her bladder two hours before the test, and again 15-30 minutes before the start thereof. The LacTEST product will be administered. From that moment, the patient should drink up to 500 ml of water to facilitate diuresis and will collect the urine in a suitable vessel for the 5 hours and will empty his/her bladder before the end of the test. This will allow determining the total amount of xylose in accumulated urine of 0 to 5h. If the patient vomits during the performance of the test, it is necessary to repeat it. If it is necessary to repeat the procedure, it must not be done until at least 3 days have passed.

For patient preparation, see section 4.4.

For instruction on reconstitution of the medicinal product before administration and instruction for use, see section 6.6.

### **4.3. Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Galactosemia
- Pentosuria.
- Patients that have a serious kidney disease, portal hypertension (ascites, cirrhosis), myxedema (severe hypothyroidism), diabetes mellitus or have medical records of total gastrectomy and/or vagotomy.

### **4.4. Special warnings and precautions for use**

#### Paediatric population

For information on the use in paediatric population, see section 4.2.

#### Patient preparation

During the performance of the test in urine, the patients will be asked to drink up to 500 ml of water to facilitate diuresis. The patients must fast from 10 hours before the test starts and during its performance. As both aspirin and indomethacin have been reported to diminish urinary excretion of xylose, subjects will be asked to avoid taken either of these drugs from at least 48 h before performance of the gaxilose test to until the test is completed

#### Specific warnings

Since urinary elimination of xylose may be reduced in patients with impairment renal function, it is mandatory to evaluate patients to detect any potential renal dysfunction when this impairment is suspected. The use of LacTEST is not recommended in patients whose glomerular filtration rate (GFR) is lower than 90

ml/min/1.73m<sup>2</sup> (see section 4.2.). If the patient vomits during the performance of the test, it is necessary to repeat it. This cannot be done until 3 days have passed.

#### **4.5. Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

Both aspirin and indomethacin have been reported to diminish urinary excretion of xylose thus; subjects will be requested to avoid the intake of any of these drugs from at least 48 h before LacTEST 0.45 g intake and until the completion of the test.

The possibility of interaction between LacTEST 0.45 g and the food containing arabinose cannot be completely discarded, therefore the patients will be warned of avoiding the intake of foods containing arabinose at least 10 hours (maximum 24 hours) before LacTEST 0.45 g intake and until the completion of the test.

#### Paediatric population

Interaction studies have only been performed in adults.

#### **4.6. Fertility, pregnancy and lactation**

##### Pregnancy

No effect during pregnancy is anticipated, since systemic exposure to gaxilose is negligible.

LacTEST can be used during pregnancy.

##### Breastfeeding

No effect during breastfeeding is anticipated, since systemic exposure to gaxilose is negligible.

LacTEST can be used during breastfeeding.

#### **4.7. Effects on ability to drive and use machines**

LacTEST has no or negligible influence on the ability to drive and use machines.

#### **4.8. Undesirable effects**

The gaxilose clinical program consists of 3 studies, representing 540 subjects who received oral gaxilose (113 mg – 5.4 g) and 12 received placebo. The tests using gaxilose investigated in this study seems to show an acceptable safety profile in healthy volunteers and the intended population. No treatment related serious adverse, nor events resulting in withdrawal, were detected. Only 13 adverse events were considered as probably or possibly related to the product under investigation, and none of them led to withdrawal. Four of them were moderate in intensity (pruritus and urticaria) and 9 were mild (abdominal distension, abdominal pain, vomit, diarrhea, nausea and migraine).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked

to report any suspected adverse reactions via Spanish Pharmacovigilance System of Human Medicines: [www.notificaRAM.es](http://www.notificaRAM.es)

#### **4.9. Overdose**

Due to the fact that only 0.45 g of gaxilose is ingested, an overdose is not expected.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Other diagnostic agents, ATC code: VO4CX.

No pharmacodynamic activity has been described for the amount of 0.45 g of gaxilose.

LacTEST is a non-invasive method which allows evaluating the overall activity of intestinal lactase *in vivo* by means of the colorimetric determination of xylose in urine or blood after the oral administration of 4-O- $\beta$ -D-galactopyranosyl-D-xylopyranose (gaxilose), a disaccharide produced by means of enzymatic synthesis which works as a structural analog of lactose, the physiological substrate of intestinal lactase. Alternatively, xylose in urine samples can also be measured by an enzymatic method. After its oral administration, gaxilose is hydrolyzed by the intestinal mucosa enzyme into galactose and xylose, and these physiological hydrolysis products pass into the blood. The appearance of xylose in urine is closely correlated with the levels of intestinal lactase activity determined post-mortem in experimental animals, therefore, the use of gaxilose allows evaluating *in vivo* the activity of this enzyme.

The critical point for classifying patients as having normolactasia or hypolactasia by means of this diagnostic test is the following: the patients with a total amount of xylose excreted in urine of 0-5 hours equal to or greater than 37.87 mg of xylose are considered as having normolactasia, if xylose is determined by the phloroglucinol method. If xylose is quantified by means of the enzymatic method, patients are considered as normolactasic when the amount of xylose in urine of 0-5 hours is equal to or greater than 19.18 mg. If the amount of xylose is lower than the previous value the patient will be considered as having hypolactasia.

#### **5.2. Pharmacokinetic properties**

After its oral administration oral, this compound is hydrolyzed by the intestinal mucosa enzyme into galactose and xylose, and these physiological reaction products pass into the blood.

##### Absorption

Gaxilose is not absorbed by the intestinal mucosa as it has been previously described. This compound is hydrolyzed by intestinal lactase into its monosaccharide constituents galactose and xylose, which are absorbed by the intestinal mucosa, carried to the blood and one of them, xylose, is eliminated in the urine.

##### Distribution

The product is hydrolyzed by intestinal lactase into galactose and xylose which, after being absorbed, pass into the bloodstream and undergo normal physiological pathways. Galactose is transformed into glucose in the liver and xylose is partially metabolized in an endogenous manner [about 50% of the ingested xylose regardless of the dose and age, demonstrated in experimental animals], and the rest appears in blood and is finally eliminated in the urine. The non-hydrolyzed disaccharide is eliminated through the intestine.

##### Metabolism

For the assessment of the metabolization rate of gaxilose and of the extent in which the xylose produced is metabolized, it was previously necessary to study the assimilation of xylose in rats at 15, 18 and 30 days of age evaluating the proportion in which this monosaccharide is recovered in urine. It was observed that approximately 48% of the xylose administered is eliminated in urine.

A Clinical Trial, performed in 12 healthy volunteers (which received 113, 225, 450, 900, 2700 and 5400 mg of gaxilose and placebo), clearly showed that the ingestion of gaxilose was followed by the appearing of xylose in blood and urine, in such a way that it depended on the oral dose administrated. This evidences that the synthetic disaccharide is a substrate in vivo of the intestinal lactase activity in human beings and that it can be used for the non-invasive evaluation of this enzymatic activity. The minimum dose of gaxilose for a reliable detection of xylose in the urine was 450 mg, to guarantee that a sufficient amount of eliminated xylose is collected.

### Elimination

Xylose is passively absorbed in the small intestine and although a portion of it is metabolized (as has been indicated above), the rest is eliminated in the urine.

### Renal/Hepatic impairment

The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.

### **5.3. Preclinical safety data**

The assays at different doses in animals have not detected toxicity at large doses. The lethal dose 50 in rats and mice both by oral route and by intravenous route was greater than 4000 mg/kg.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

None.

### **6.2. Incompatibilities**

This medicinal product must not be mixed with other medicinal products.

### **6.3. Shelf life**

Unopened sachets: 2 years.

After reconstitution, the suspension should be used immediately

### **6.4. Special precautions for storage**

Unopened sachets. This medicinal product does not require any special temperature storage conditions.

Keep the sachets in the outer carton.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5. Nature and contents of container

Pack size of one sachet for single use.

Sachets formed by a PVC sheet and an Alu/Surlym/Opaline sheet, containing 0.45g gaxilose

## 6.6. Special precautions for disposal and other handling

Carefully dissolve the entire contents of the sachet in about 100 ml of water. A clear and colourless solution will be obtained. The patient must immediately drink this solution and the time of the ingestion must be recorded. The total urine from 0 to 5 hours will be collected.

The measurement of xylose levels in the 0-5 hours collected urine samples may be performed both using the enzymatic kit with the automated analyzers or making use of the phloroglucinol manual technique described hereinafter. Patients with a total amount of xylose excreted in urine of 0-5 hours greater than or equal to 19.18 mg of xylose, using the enzymatic kit, and 37.87 mg of xylose, quantified making use of the manual phloroglucinol method, are considered normolactasic. Should the amount of xylose is less than the previous values (according to the method used), the patient will be considered hypolactasic.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### Analysis of samples and specification of the assay for laboratories

#### **Xylose determination using the enzymatic kit with automated analyzers**

The enzymatic kit for xylose quantification includes the following reagents:

**Vial 1.** Phosphate buffer 50 mM, pH 8.0 (solution)

**Vial 2.** Lyophilized NAD<sup>+</sup>

**Vial 3.** Lyophilized Xylose dehydrogenase enzyme

**Vial 4.** Calibrator: Standard xylose solution (3.75 mg/dl)

#### **Preparation of Kit reagents**

Important: reagents preparation must be carried out in the following position.

1. Add phosphate buffer (vial 1) in the vial 3, to dissolve the enzyme lyophilized at a final concentration of 0.24 mg/ml. Mix gently to avoid loss of activity in the suspended enzyme. Keep cold during use if possible. This will be called **REACTIVE 2**.
2. Add phosphate buffer (vial 1) in the vial 2 (lyophilized NAD<sup>+</sup>) and mix until it is totally dissolved (vortex if necessary).
3. Add the complete dissolved NAD<sup>+</sup> (NAD<sup>+</sup> + buffer) to the vial 1 Thus, the vial 1 will contain phosphate buffer plus NAD<sup>+</sup> in the appropriated concentration for the assays (3.4 mg/ml). Keep cold during use if possible. This will be called **REACTIVE 1**.
4. The Standard xylose solution is ready for use.

#### **Automated analyzer assay protocol:**

**Sample preparation:** Every urine sample must be shaken after thawing and centrifuged in order to homogenize it and remove any precipitate that could affect the assay.

**Instrument settings:** Reaction kinetics with two reagents (R1 and R2), reaction endpoint, wavelength 340 nm. Reaction will be carried out at the standard device temperature (usually 37°C). The instrumental application for testing must be designed and incorporated by the technical manager of the team, according to the following specifications:

## GENERAL ANALYZER ASSAY PROTOCOL:

In this protocol, the final volume of the reaction ( $V_R$ ) is the addition of the volumes of reactive 1, reactive 2 and distilled water (for the blank), sample or xylose calibrator.

Step	Reactive	Blank	Calibrator	Sample
1	Distilled water	$0.175 \times V_R \mu\text{l}$	-	-
	REACTIVE I (phosphate buffer +NAD <sup>+</sup> )	$0.725 \times V_R \mu\text{l}$	$0.725 \times V_R \mu\text{l}$	$0.725 \times V_R \mu\text{l}$
	Sample (Urine)	-	-	$0.175 \times V_R \mu\text{l}$
	Xylose Calibrator (3.75 mg/dl)	-	$0.175 \times V_R \mu\text{l}$	-
Mix the reaction and incubate for 5 min. After this, read the absorbance (A1)				
2	REACTIVE 2 (Xylose dehydrogenase)	$0.1 \times V_R \mu\text{l}$	$0.1 \times V_R \mu\text{l}$	$0.1 \times V_R \mu\text{l}$
Mix the reaction, incubate for 5 min and read the final absorbance (A2)				
Note: Each time xylose is measured in urine samples, xylose controls must be performed after calibration. These controls, one with low concentration and the second with high concentration, must be measured as if they were samples.				

Example for  $V_R = 200 \mu\text{l}$ :

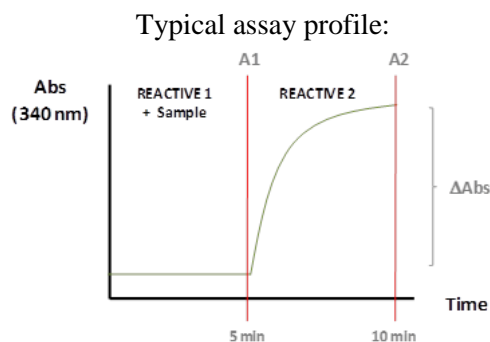
Step	Reactive	Blank	Calibrator	Sample
1	Distilled water	35 $\mu\text{l}$	-	-
	REACTIVE I (phosphate buffer +NAD <sup>+</sup> )	145 $\mu\text{l}$	145 $\mu\text{l}$	145 $\mu\text{l}$
	Sample (Urine)	-	-	35 $\mu\text{l}$
	Xylose Calibrator (3.75 mg/dl)	-	35 $\mu\text{l}$	-
Mix the reaction and incubate for 5 min. After this, read the absorbance (A1)				
2	REACTIVE 2 (Xylose dehydrogenase)	20 $\mu\text{l}$	20 $\mu\text{l}$	20 $\mu\text{l}$
Mix the reaction, incubate for 5 min and read the final absorbance (A2)				

Note: Each time xylose is measured in urine samples, xylose controls must be performed after calibration. These controls, one with low concentration and the second with high concentration, must be measured as if they were samples.

**Observation: the shown protocol has been designed according to general specifications. However, final volumes and dilutions of reactives might be different among analyzers, as long as their final concentrations and ratios are maintained in the final assay mixture (2.46 mg/ml of NAD<sup>+</sup>, 0.024 mg/ml of xylose dehydrogenase, phosphate buffer 50 mM).**

### Calculations:

#### Total amount of xylose in urine samples



Two values of Absorbance (340 nm) will be recorded from each assay:

- A1 = initial Absorbance of the mix **REACTIVE 1** + Sample (incubated 5 min)
- A2 = final Absorbance after addition of **REACTIVE 2** (incubated 5 min)

Differences between the two Absorbance values are proportional to xylose concentration which could be calculated using the provided xylose standard solution as reference:

- $\Delta\text{Absorbance (340 nm)} = \Delta\text{Abs} = \text{A2} - \text{A1}$
- Concentration of xylose in Sample (Urine) =  $[\text{Sample}] \text{ (mg/dl)}$
- Concentration of xylose in Standard solution =  $3.75 \text{ mg/dl}$

$$[\text{Sample}] \text{ (mg/dl)} = \frac{\Delta\text{Abs (Sample assay)}}{\Delta\text{Abs (Calibrator)}} \times 3.75 \text{ mg/dl}$$

The total amount of xylose in the Sample (mg) will be calculated from its total volume:

$$\text{Xylose (mg)} = [\text{Sample}] \text{ (mg/dl)} \times \text{Volume Sample (dl)}$$

### Example:

Determination of Total amount of xylose in an urine sample:



- Total volume of sample (urine) = 557 ml = 5.57 dl

1) Sample assay: A1 = 0.122  
A2 = 0.146

$$\Delta Abs (\text{Sample assay}) = 0.146 - 0.122 = 0.024$$

2) Standard assay: A1 = 0.087  
A2 = 0.166

$$\Delta Abs (\text{Calibrator}) = 0.166 - 0.087 = 0.079$$

$$[\text{Sample}](\text{mg/dl}) = \frac{0.024}{0.079} \times 3.75 \text{ mg/dl} = 1.139 \text{ mg/dl}$$

$$\text{Xylose (mg)} = 1.139 \frac{\text{mg}}{\text{dl}} \times 5.57 \text{ dl} = \mathbf{6.34 \text{ mg}}$$

### Normal values in adults

Test	Xylose in urine (mg)
LacTEST 0.45 g	≥ 19.18

Values below 19.18 mg are considered indicative of hypolactasia.

Note:

Considerations to be taken into account concerning the urine samples storage

- 1- It is recommended to store the urine samples for the measurement of xylose, at 4°C if the determination is going to be carried out on the day; or otherwise, when the measurement is not being performed on the day, samples should be stored at -20°C or -70°C (samples will remain stable at least 2 months after freezing).
- 2- If measurements need to be repeated, samples can be frozen and thawed at least three times in a period of 2 months.

### Validation of xylose quantification method in urine using the enzymatic kit

Analytical parameters(*)	
Range of the calibration curve	From 0.25 to 15 mg/dl
Linearity	$r^2 \geq 0.9996$
Limits	Limit of Blank: 0.046 - 0.072 mg/dl Limit of Detection: 0.13 - 0.49 mg/dl Limit of Quantification: 0.42 - 1.64 mg/dl
Precision (coefficients of variation)	Within-run precision < 13.6% Between-run precision < 11.5%
Accuracy (percent of the nominal value)	Within-run accuracy ≤ 17.2% Between-run accuracy ≤ 5.9%
Carry-over	3.3 - 4.0%

(\*) Range of data calculated from 3 different automatic analyzers.

Note: Before implementing the enzymatic test into a specific analyzer, analytical validation must be performed following the approved current Guidelines.

### **Xylose quantification using manual phloroglucinol method**

It consists of the spectrophotometric determination of a coloured compound formed between the reagent phloroglucinol (1,3,5-OH-benzene) and furfural, which is the product of the reaction of xylose in a strongly acidic medium.

A validated protocol for determination of xylose in urine samples of patients, who received LacTEST 0.45 g, including recommendations for treatment and storage of samples, is indicated below.

### **Xylose Determination Protocol**

Prepare:

- a) 6.66 mM solution of xylose (100 mg/dl) in Milli Q water. From this solution, a 0.66 mM (10 mg/dl) solution, which will be used in the calibration curves, is prepared.
- b) Colour reagent with phloroglucinol.
  - 0.5 g of phloroglucinol
  - 100 ml of glacial acetic acid
  - 10 ml of hydrochloric acid.

The resulting mixture is enough to process 50 samples (50 tubes) and it should be prepared fresh before its use. Once it has been prepared the reaction mix should not be used for more than 5 hours.

- c) Prepare a xylose standard curve ranging from 0.0125 to 0.5 mg/dl (0.25 to 10 µg).

The standard curve is expressed both in mg/dl and in µg of xylose, since the value of xylose in urine is expressed as the total amount (mg) referred to the volume of urine collected for each subject (amount units are used because the diagnosis in urine is expressed as the total amount of xylose present in urine). The standard xylose solution should be prepared fresh on the day when the xylose measurements are performed. Once it has been prepared the standard solution should be used within 5 hours.

	<b>Xylose Standard Curve</b>								<b>Samples</b>			
Xylose, mg/dl	0	0.0125	0.025	0.05	0.1	0.2	0.4	0.5				
Xylose, 10 mg/dl (µl)	-	2.5	5	10	20	40	80	100	-	-	-	-
Urine (µl)	-	-	-	-	-	-	-	-	25	50	75	100
Milli Q water (µl)	100	97.5	95	90	80	60	20	-	75	50	25	0
Phlorogl. reagent (ml)	1.9 ml	→							→			

- 10 ml Polypropylene tubes, acids and heat resistant, are used. The samples are added. A xylose standard curve is made, with the xylose amounts indicated above.
- The phloroglucinol reagent is added to each tube until completing a volume of 2 ml.
- Tubes are incubated in a 100°C bath for 4 minutes exactly and then cooled in water.
- The absorbance at 554 nm is measured in a colorimeter or spectrophotometer immediately after cooling the reaction.
- The spectrophotometer is adjusted to zero absorbance, before reading the standard solutions and samples, with a reagent blank containing water and phloroglucinol reagent. This “reagent blank” is heated and cooled along with the other samples.
- Calculation: The concentration of xylose in urine is calculated extrapolating the values from the calibration curve. The total volume of urine collected during 5 hours after intake of the product needs to

be recorded, to calculate the total amount of xylose in the 5-hours urine.

### Normal values in adults

Test	Urine xylose (mg)
LacTEST 0.45 g	$\geq 37.87$

Values below 37.87 mg are considered indicative of hypolactasia.

Note:

Considerations to be taken into account concerning the urine samples storage:

1. It is recommended to store the urine samples for the measurement of xylose, at 4°C if the determination is going to be carried out on the day; or otherwise, when the measurement is not being performed on the day, samples should be stored at -20°C or -70°C (samples will remain stable at least 2 months after freezing).
2. If measurements need to be repeated, samples can be frozen and thawed at least three times in a period of 2 months.

Regarding work solutions and processed samples of urine, the following aspects should be considered:

1. The colour reagent of phloroglucinol is only stable for 5 hours after its been mixed.
2. Once samples have been processed by heating in the presence of the phloroglucinol reagent, samples will only be stable during the first three hours, after processing.

### Validation of the method of measurement of xylose in urine with the manual phloroglucinol method.

Calibration Curve Range:	0.5 – 20 mg/dl
Linearity:	$y = 1.2225x + 0.0095$ $r^2 > 0.9997$
Sensitivity:	Quantification limits for urine and serum samples is at 0.5 mg/dl.
Reproducibility:	CVs between different samples must not be greater than 15%.
Accuracy:	CVs between different samples must not be greater than 15%.
Measurement error:	0.48 – 6.45%

Sensitivity and specificity values of the phloroglucinol and enzymatic xylose detection methods.

Method	Sensitivity	Specificity	Reference method
Phloroglucinol method	0.935	0.918	Biopsy
Enzymatic method	0.955	0.993	Phloroglucinol method

## 7. MARKETING AUTHORISATION HOLDER

Venter Pharma S.L.  
Azalea, 1  
28109 Alcobendas-Madrid  
Spain

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the Spanish Agency for Medicines and Medical Devices (AEMPS) [http:// www.aemps.gob.es](http://www.aemps.gob.es)