

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PULMISTAT[®] 7,5 mg/5 ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Each 5 ml syrup contains 7.5 mg butamirate citrate (1.5 mg/ml).

List of excipients: In each 5 ml;

Sodium saccharine dihydrate	1.00 mg
Carboxymethyl cellulose sodium	5.00 mg
Glycerin	750 mg
Sorbitol (E420)	2750 mg
Benzoic acid (E210)	4.25 mg
Sodium hydroxide	q.s.. pH: 3,5-4,5

For the list of excipients see 6.1

3. PHARMACEUTICAL FORM

Syrup

Colorless, clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

PULMISTAT[®] is indicated in the following conditions:

- Acute cough due to different etiologies
- Cough relief before or after surgical interventions or bronchoscopy

4.2. Posology and method of administration

Posology/The duration and frequency of administration:

Children between 6 and 12 years of age: 10 ml, three times daily

Adolescents over 12 years of age: 15 ml, three times daily

Adults: 15 ml, four times daily

Unless prescribed by a doctor, the maximum treatment time is 1 week (see section 4.4 Special warnings and precautions for use)

Method of administration:

To be taken orally.

The measuring spoon should be cleaned and dried after each use.

Additional information on special populations:

Renal/Hepatic failure:

Use of butamirate citrate in patients with renal or hepatic failure has not been investigated.

Pediatric population:

PULMISTAT[®] is contraindicated in children under 3 years of age. Its use in children under 6 years of age is not recommended.

Geriatric population:

Use of butamirate citrate in the elderly has not been tested.

4.3. Contraindications

PULMISTAT[®] is contraindicated in subjects with known hypersensitivity to butamirate citrate or other ingredients.

Contraindicated in children under 3 years of age.

4.4 Special warnings and precautions for use

Since butamirate citrate inhibits the cough reflex, concomitant use of expectorating medicines may lead to mucus retention in the respiratory system, leading to an increased risk of bronchospasm and airway infection. Thus simultaneous use of PULMISTAT[®] with expectorating agents should be avoided.

Its use is not recommended in children under 6 years of age.

Talk to your doctor or pharmacist if cough persists for more than 7 days.

PULMISTAT[®] contains sorbitol. Individuals with the rare fructose intolerance should not take this medicine.

Also this medicinal product contains benzoic acid. However no unwanted effects are expected due to its route of administration.

PULMISTAT[®] contains less than 10 g of glycerin in a 5 ml dose. No adverse effects due to glycerin is expected due to its dose.

This medicinal product contains less than 1 mmol (23 mg) of sodium in each dose; in other words, adverse effects due to sodium are unlikely.

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

Concomitant use of expectorating agents should be avoided (see 4.4).

4.6. Pregnancy and lactation**General recommendation**

Pregnancy category: B

Women of childbearing potential/Contraception

No adequate animal studies have been carried out to examine the effect on pregnancy and/or fetal/embryonic development and/or birth or postnatal development (see Section 5.3). Potential risk in humans is unknown.

Since the effect of butamirate citrate on the fetus and newborn are not completely known, patients should use a proper method of contraception when taking this medicine.

Pregnancy

No clinical data exists on exposure to butamirate citrate during pregnancy.

Use of PULMISTAT[®] should be avoided in the first trimester of the pregnancy. After the first trimester, PULMISTAT[®] should only be used during pregnancy when absolutely necessary.

Lactation

It is unknown whether butamirate citrate and/or its metabolites are secreted into the breast milk. The decision to stop breast-feeding or PULMISTAT[®] treatment, or to avoid/stop the treatment should be based on the balance between the benefits of breastfeeding for the infant and the benefit of PULMISTAT[®] treatment for the lactating mother.

Reproduction/Fertility

No safety risks have been observed in reproductive toxicity studies (see. Section 5.3 Pre-clinical safety data)

4.7. Effects on ability to drive or use machines

PULMISTAT[®] may cause drowsiness. Therefore care should be taken when driving or using machinery during its use.

4.8. Undesirable effects

The frequency of adverse effects is classified as follows:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1.000$ to $< 1/100$); rare ($\geq 1/10.000$ to $< 1/1.000$); very rare ($< 1/10.000$), unknown (cannot be estimated based on existing data).

Nervous system disorders

Rare: Sleepiness

Gastrointestinal disorders

Rare: Nausea, diarrhea

Skin and subcutaneous tissue disorders

Rare: Urticaria

Reporting of suspicious adverse reactions

Post-marketing reporting of suspicious drug reactions is very important for continuous monitoring of the benefit/risk ratio of a medication. Healthcare professionals should report any suspicious adverse reactions to Turkish Pharmacovigilance Center (TÜFAM): (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose and treatment

PULMISTAT[®] overdose may lead to symptoms such as sleepiness, nausea, vomiting, diarrhea, dizziness and hypotension.

General measures of emergency treatment should be followed: gastric lavage, activated charcoal, monitoring and –if required- treatment of vital functions. There are no known specific antidotes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cough suppressants

ATC code: R05DB13

The active ingredient of PULMISTAT[®], butamirate citrate, is a cough suppressant that is chemically and pharmacologically unrelated to opium alkaloids.

Mechanism of action

Although the active ingredient is thought to exert central effects, its exact mechanism of action is not fully understood. Butamirate citrate has non-specific anticholinergic and broncho-spasmolytic effects that alleviate respiratory functions. PULMISTAT[®] does not cause dependency or habit formation.

Butamirate citrate has a wide therapeutic window. PULMISTAT[®] is well tolerated even in higher doses, and is a suitable therapeutic option for reducing the cough in children over 6 years of age and adults.

5.2 Pharmacokinetic properties

Absorption:

Based on the existing data, it may be assumed that butamirate when administered orally is absorbed quickly and completely and hydrolyzed mainly to phenyl-2 butyric acid and diethylaminoethoxyethanol. The effect of food on absorption has not been investigated. The exposure to phenyl-2 butyric acid and diethylaminoethoxyethanol is fully dose-proportional in the dose range between 22.5 mg and 90 mg.

Following oral administration butamirate citrate is rapidly absorbed and measurable blood concentrations are reached within 5 to 10 minutes after administration of 22.5, 45, 67.5 or 90 mg doses. For all doses, the maximum plasma concentrations are reached within 1 hour, with an average concentration of 16.1 nanogram/ml for the 90 mg dose.

The average maximum plasma concentration of the major metabolite phenyl-2 butyric acid is reached after 1.5 hour with a 90 mg dose (3052 nanogram/ml). Maximum average plasma concentrations are reached within 0.67 hours for diethylaminoethoxyethanol.

Distribution:

Butamirate citrate, in addition to high protein binding, exhibits a wide volume of distribution between 81 and 112 L (per kg body weight). Phenyl-2 butyric acid is highly (89.3-91.6%) protein bound in all doses (22.5 to 90 ml). Diethylaminoethoxyethanol exhibits a certain degree of protein binding (28.8 to 45.7%). Placental transfer or secretion into human breast milk of butamirate citrate is unknown.

Biotransformation

Hydrolysis of butamirate citrate to phenyl-2-butyric acid and diethylaminoethoxyethanol is rapid and complete. Based on studies involving different species, both major metabolites are thought to have antitussive effects. No human data is available for the alcohol metabolite. C-14 studies in humans showed high plasma protein binding (approx. 95%, only phenyl-2-butyric acid could be demonstrated due to methodological issues). Phenyl-2-butyric acid also undergoes partial biotransformation through hydroxylation in para position.

Elimination:

The three metabolites are mainly excreted through the kidneys. Following the conjugation in liver, the acid metabolites are connected to the glucuronic acid, widely.

Urinary 2-phenyl-butyric acid conjugate concentrations are much higher compared to plasma. Butamirate citrate can be detected in urine for up to 48 hours, and the proportion of butamirate citrate excretion in the 96-hour sampling period for 22.5, 45 mg, 67.5 mg, and 90 mg doses are 0.02%, 0.02%, 0.03% and 0.03%, respectively. As compared to butamirate or unconjugated 2-phenylbutyric acid, a significant proportion of butamirate citrate is excreted into the urine in the form of diethyl-amino-ethoxyethanol. The measured elimination half-life for 2-phenylbutyric acid, butamirate, and diethyl-aminoethoxyethanol are 23.26 - 24.42, 1.48-1.93 and 2.72-2.90 hours.

Characteristic patient populations

The effect of hepatic or renal dysfunction on pharmacokinetics of butamirate citrate is unknown.

5.3 Preclinical safety data

No specific toxic effects in humans are expected based on conventional safety, pharmacology, repeat dose toxicity, genotoxicity, carcinogenicity, and reproduction/development toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium saccharin dihydrate
Carboxymethyl cellulose sodium
Benzoic acid (E210)
Glycerin
Sorbitol (E420)
Apricot flavor
Sodium hydroxide (for pH adjustment when necessary)
Hydrochloric acid (for pH adjustment when necessary)
Purified water

6.2 Incompatibilities

None known.

6.3. Shelf life

24 months

6.4 Special precautions for storage

Store in room temperature below 25°C.

6.5 Nature and contents of container

Primary packing: amber colored 100 ml glass bottle with a plastic pilfer-proof cap and with 5 ml measuring spoon.

6.6. Disposal of medicinal waste and other special precautions

It should be disposed in accordance with the “Directive for the Control of Medicinal Waste” and “Directive for the Control of Packing and Packing Waste”.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

2015/236

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 05 March 2015

Renewal of the latest authorization:

10. DATE OF REVISION OF SMPC

Date of SMPC approval: