SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SINECOD Syrup 7.5 mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Butamirate Citrate **7.5 mg/5 ml**

Butamirate Citrate: $C_{24}H_{37}NO_{10}$
2-[2-(diethylamino)-ethoxy]ethyl-2-phenylbutyrate Citrate

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Syrup

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dry non-productive cough

4.2 Posology and method of administration

The usual dose is

Adults:

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

Children aged 4-6 years of age: 5 ml three times daily
Children aged 6-12 years of age: 10 ml three times daily

If possible SINECOD® must be taken before meals.

The syrup contains saccharin and sorbitol sweeteners; therefore it may be used by diabetics

4.3 Contra-indications

Use of SINECOD is not recommended in cases of hypersensitivity to butamirate citrate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Because butamirate inhibits the cough reflex simultaneous administration of expectorants should be avoided, because it may lead to the stagnation of mucus in the respiratory tract, which can increase the risk of bronchospasm and airway infection.

You should talk to your doctor if the cough persists for more than 7 days.

Information concerning excipients

Sorbitol (E 420): Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Ethanol: This medicinal product contains small amounts of ethanol (11.73 mg/5ml), less than 100 mg per dose.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous administration of expectorants should be avoided (see 4.4. Special warnings and precautions for use).

4.6 Pregnancy and lactation

Use during pregnancy:

Reproductive studies in animals have shown no risk for the foetus. However, as there are no sufficient studies in pregnant women, the use of SINECOD should be avoided during the first trimester of pregnancy. For the following months of pregnancy, Sinecod should be used according to the doctor's judgement and instructions.

Use during breast-feeding:.

Because there is insufficient information on the excretion of butamirate in human milk, for safety reasons SINECOD should be used during breast-feeding only after a careful evaluation of benefits compared with the potential risk.

4.7 Effects on ability to drive and use machines

SINECOD® may cause drowsiness in rare cases. It may have a minor influence on the ability to drive and use machines. Therefore it must be taken into account when driving or performing other tasks requiring alertness (e.g. operating machines)

4.8 Undesirable effects

Nervous system disorders

Rare (>1/10,000, <1/1000): drowsiness

Gastrointestinal disorders

Rare (>1/10,000, <1/1000): nausea, diarrhoea

Skin and subcutaneous tissue disorders

Rare: (>1/10,000, <1/1000): urticaria.

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: http://www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

In case of an accidental overdose, the following symptoms may appear: drowsiness, nausea, vomiting, diarrhoea, loss of balance and hypotension.

The usual direct measures that must be taken are:

Gastric lavage, administration of activated charcoal, **monitoring and treatment of the vital functions if required. There is no known specific antidote.**

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherpeutic group: R05DB13

Other antitussives/Butamirate

5.1 Pharmacodynamic properties

Butamirate citrate, the active ingredient of SINECOD, suppresses the cough without being chemicallyor pharmacologically related to opium alkaloids.

The substance is thought to have central action. The exact mechanism of action is unknown. Butamirate citrate presents a non-specific anticholinergic and antispasmodic effect which facilitates respiration . Sinecod does not induce dependence or addiction.

Butamirate citrate has a broad therapeutic range. It is well tolerated even at high doses and well suited for cough relief in adults and children.

Butamirate citrate is a non-narcotic antitussive which acts at the centre of the cough. Unlike morphine products (narcotic antitussives), SINECOD®® lacks the risk of their side effects without lacking the antitussive action.

5.2 Pharmacokinetic properties

Absorption

Butamirate when administered orally is absorbed quickly and completely. It is hydrolysed mainly into phenyl-2-butyric acid and diethylaminoethoxyethanol. The influence of food ingestion has not been investigated. Exposure to phenyl-2-butyric acid and diethylaminoethoxyethanol is fully proportional across the dose range of 22.5 mg – 90 mg.

When administered orally, butamirate is rapidly absorbed. It can be detected in the blood plasma within 5 to 10 minutes of administration of a 22.5 mg, 45 mg, 67.5 mg and 90 mg dose. Maximum plasma concentrations are reached after one hour for all four dose levels, with a mean value of 16.058 ng / ml at the dose of 90 mg.

The mean plasma concentration of phenyl-2-butyric acid is reached within 1.5 hours with the greatest exposure being observed after 90 mg (3.052 nanogram / mL). The mean plasma concentration of diethylaminoethoxyethanol is reached within 0.67 hour again with greatest exposure again being observed after 90 mg (160 nanograms / ml).

Distribution

Butamirate has a high volume of distribution ranging between 81 and 112 L (depending on body weight in kg) as well as a high degree of protein binding. Phenyl-2-butyric acid is highly protein bound in plasma across all dose levels (22.5 – 90 mg) with mean values of 89.3% – 91.6%. Diethylaminoethoxyethanol exhibits some degree of protein binding with mean values ranging between 28.8% – 45.7%. It is not known whether butamirate crosses the placenta or whether it is secreted in human milk.

Metabolism

The hydrolysis of butamirate, which leads mainly to phenyl-2-butyric acid and diethylaminoethoxyethanol, takes place immediately and completely. Based on studies in various species, it is concluded that the main metabolites have an antitussive effect. There are no human data on the alcoholic metabolite. Phenyl-2-butyric acid undergoes further partial metabolisation through hydroxylation at position p.

Elimination

The excretion of the three metabolites takes place primarily via the kidneys; following conjugation in the liver, the acid metabolite is subject to large-scale binding to glucuronic acid. Urinary 2-phenylbutyric acid conjugate levels are much higher than in plasma. Butamirate can be detected in the urine for up to 48 hours and the amount of butamirate excreted in urine over the 96-hour sampling period, accounts for approximately 0.02, 0.02, 0.03 and 0.03% of the 22.5 mg, 45 mg, 67.5 mg and 90 mg dose levels, respectively. A greater percentage of the butamirate dose is excreted in the urine in the form of diethylaminoethoxyethanol or unconjugated phenyl-2-butyric acid. The average measured half-lives of phenyl-2-butyric acid, butamirate, and diethylaminoethoxyethanol are 23.26–24.42, 1.48–1.93, and 2.72–2.90 hours, respectively.

Pharmacokinetic properties in special patient groups

There are no known effects of hepatic or renal function disorders on the pharmacokinetic parameters of butamirate.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol sol., glycerol, saccharin sodium, benzoic acid, vanillin, ethanol sol., sodium hydroxide sol., water purified.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at 25 ^{o}C or below

6.5 Nature and contents of container

Glass bottle containing 200 ml or 250 ml of syrup.
Package includes a measuring cup.

6.6 Special precautions for disposal and other handling

Clean the cup thoroughly after each use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

MA1177/00101

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20th April 2007 / 08th October 2012

10. DATE OF REVISION OF THE TEXT

14th August 2024