MUSCORIL®
Thiocolchiside
Injection and capsules

sanofi aventis

COMPOSITION
MUSCORIL Injection
Each ml sol Injection contains
Thiocholchiside..... 2 mg

MUSCORIL Capsule
Each capsules contains
Thiocolchiside..... 4 mg

CLINICAL DATA

Therapeutic indications
Symptomatic tratment of the painful muscular spasm in simple how low back pain.

Dosage and method of administration

- Recommended dosage and duration of administration:

  - Intramuscular route: one 4 mg ampoule bid for 3 to 5 days.
  - Oral route: two 4 mg capsules bid for 5 to 7 days.

- Administration scheme

Severe muscular contracture:
- The treatment will be initiated by the intramuscular route at the dosage of one 4 mg ampoule bid for 3 to 5 days, and eventually continued by the oral route at the dosage of two 4 mg capsules bid for 5 to 7 days.

Mild to moderate muscular contracture:
- Two 4 mg capsules bid for 5 to 7 days.

Contra-indications
- Hypersensitivity to thiocolchiside or one of its excipients.
- Pregnancy and Lactation (see Pregnancy and Lactation).

Special warnings and special precautions for use
- Thicolchiside is not reccomended for use in children.
- Reduce the dosage, as necessary, in case of diarrhea.

Interactions with other medicial products and other forms of interaction
Not known

Pregnancy and Lactation

- Studies conducted in animals have shown a reproductive toxicity (see Preclinical safety data).
In humans, there is no pertaining data for a use of thiocolchicoside in pregnant women. Thus, the potential hazards for the embryo and fetus are unknown. In consequence, thiocolchicoside should not be used during pregnancy (see Contraindication).

- Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated in case of breastfeeding.

Effects on ability to drive and to operate machines
There are no data available of the effect on driving vehicles and using machines.
although only rare cases of drowsiness have been reported, this has to be taken into account when driving vehicles and operating machines.

Undesirable effects

- Rare cases of gastrointestinal disorders such as: diarrhoea, gastralgia, nausea, vomiting (see: Special warnings and special precaution for use).
- Rare cases of cutaneous allergic reactions, including angioedema.
- Very rare cases of anaphylactic reactions, such as hypotension or anaphylactic shock, have been reported following the intramuscular administration.
- Rare cases of drowsiness have been reported (see Effects on ability to drive and use machines)

Overdose
No overdosage symptoms have been reported in patients treated with thicolchicoside. Should overdosage occurs, medical supervision and symptomatic measures are recommended (see Preclinical safety data).

Pharmacodynamic properties
Pharmacotherapeutic group: muscle relaxant, ATC code: MO3BX03.

Thicolchicoside is a semi-synthetic sulphurated derivative of colchicoside, with myorelaxant pharmacological activity.

In-vitro, thicolchicoside only binds to GABA-A and strychnine-sensitive glycine receptors. Thiocolchicoside acting as a GABA-A receptor antagonist, its myorelaxant effects could be exerted at the supraspinal level, via complex regulatory mechanism, although a glycinergic mechanism of action can not be excluded. The characteristics of the interaction of thiocolchicoside with GABA-A receptors are qualitatively and quantitatively shared by its main circulating metabolite, the glucuronidated derivative (see Pharmacokinetic properties).

In-vivo, the myorelaxant properties of thiocolchicoside and its main metabolite have been demonstrated in various predictive models of rats and rabbits. The lack of myorelaxant effects of thiocolchicoside in spinalized rats suggests as predominant supraspinal action for this compound. Thiocolchicoside was also found to posses anti-inflammatory and analgesic activities in a variety of experimental models after oral, subcutaneous, intraperitoneal and intramuscular

administration. Moreover, in pharmaco-EEG studies, thiocolchicoside and its main metabolite were shown to be devoid of any sedative effect.

Pharmacokinetic properties
Thiocolchicoside is rapidly adsorbed after oral administration, and matabolized into 3 main metabolites. The two main circulating forms were the thiocolchicoside aglycon and the glucuronidated derivative of thiocolchicoside, which is active. The active glucoronidated derivative of thiocolchicoside is also observed after intramuscular administration.

In humans, the binding of thiocolchicoside to human serum proteins is low (13%) and not dependent on the therapeutic concentration of thiocolchicoside and serum albumin is mainly involved in serum protein binding.

After oral administration in healthy voulenteers:
No traces of thiocolchicoside are detected. The active glucuronidated metabolite appears rapidly in plasma with a median Tmax at 1 hour, and is eliminated with a mean apparent terminal half-life of about 7 hours.

After a single 8 mg oral administration of thicolchicoside, the mean area under the curve (AUC) of the active glucuronidated metabolite, which reflects exposure to the active entities, is about 126 ng.h/mL.

After oral administration of (14C)-radiolabelled thiocolchicoside, 79% of the dose is recovered in faeces and 20% in urine.

After intramuscular administration in healthy volunteers:
Both thiocolchicoside and the active glucuronidated metabolite are present. Peak plasma levels are reached in about half an hour for thiocolchicoside and 5 hours for its active glucuronidated metabolite, with mean apparent terminal elimination half lives of 1.5-1.9 hours and 9 hours, respectively.
After a single 8 mg intramuscular administration of thiocolchicoside, the mean cumulative area under curve (AUC) of thiocolchicoside and its glucuronidated metabolite, which reflects exposure to the active entities, is about 500 ng.h/mL.
The apparent volume of distribution and systematic clearence of thiocochicoside are about 43 L and 19 L/h, respectively.

Preclinical safety data
Thiocolchicoside safety profile has been assessed in vitro, an in vivo following intramuscular and oral administration. Thicolchicoside was well tolerated following oral administration for periods of up to 6 months in both the rat and the non-human primate when administered at repeated doses of less than or equal to 2 mg/kg/day in the rat and less or equal to 2.5 mg/kg/day in non-human primate, and by the intra muscular route in the primate at repeated doses up to 0.5 mg/kg/day for 4 weeks.

At higher doses, thiocolchicoside induced diarrhea and convulsions in both rodents and non rodents after acute administration by oral route. After repeated administration, thiocolchicoside induced gastro-intestinal disorders (enteritis, emesis) by oral route, and emesis by i.m. route.

The compound did not induce adverse effect on fertility. By contrast, a teratogenic effect and perinatal toxicity was demonstrated. No evidence for teratogenic effects of thiocolchicoside was described at doses up to 3 mg/kg/day. Thiocolchicoside was shown to be devoid of mutagenic potential when used at the therapeutic dose.

Incompatibilities
In the absence of the compatibility studies, the solution for injection and the content of the capsules should not be mixed with other medicinal products.

Special precautions for storage
No special precautions for storage.

Shelf-life
Ampoules: 3 years.
Capsules: 3 years.

Nature and content of container
- Ampoules:
  Type I printed colourless glass single-use 2 ml ampoules
- Capsules:
  Alumunium/opaque PVC blister packs

Instructions for use and handling and disposal
None

PRESENTATION
- Box of 6 ampoule of 2 ml sol Injection
  Reg. No. DKI.....
- Box of 2 blister of 10 Capsules
  Reg. No. DKI.....

Harus dengan resep dokter.

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