

SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 to TUFAM. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

TIORELAX® 4 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug Substance:

Each tablet contains 4 mg thiocolchicoside.

Excipient(s):

Lactose monohydrate (bovine) 33,84 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Yellow, round, biconvex tablet, debossed “4” on one face and scored on the other face. (The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses, the tablet may be divided into equal halves).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Indicated for the treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards.

4.2. Posology and method of administration

For oral use.

Posology:

TIORELAX® is used in adults at a maximum dose of 16 mg per day.

Frequency and duration of administration:

The recommended and maximal dose is 8 mg (2 tablets) every 12 hours (twice a day) (at most 4 tablets a day, i.e. 16 mg). The treatment duration is limited to 7 consecutive days.

Doses exceeding recommended doses or long-term use should be avoided (see section 4.4).

Method of application:

For oral use only.

Tablets should be taken with water on a full stomach.

If diarrhea occurs after oral administration, treatment should be discontinued.

Additional information on special populations

Renal / Hepatic Failure: The safety and efficacy of TIORELAX® have not been studied in patients with renal/hepatic failure.

Pediatric population: TIORELAX® should not be used in children and adolescents under 16 years of age because of safety concerns (see section 5.3).

Geriatric population:

The safety and efficacy of TIORELAX® have not been studied in elderly.

4.3. Contraindications

Thiocolchicoside must not be used:

- in flaccid paralysis, hypotone muscle
- in patients hypersensitive to the active substance or to any of the excipients listed in section 6.1
- during the entire pregnancy period
- during lactation
- in women of childbearing potential not using contraception.
- in children aged 16 years and under.

4.4. Special warnings and precautions for use

Preclinical studies showed that one of thiocolcoside metabolites (SL59.0955) induced aneuploidy (i.e. unequal number of chromosomes in dividing cells) at concentrations close to human exposure observed at doses 8 mg twice daily per os (see section 5.3). . Aneuploidy is considered as a risk factor for teratogenicity, embryo/foeto-toxicity, spontaneous abortion, and impaired male fertility and a potential risk factor for cancer. As a precautionary measure, use of the product at doses exceeding the recommended dose or long-term use should be avoided (see section 4.2).

Post marketing cases of cytolytic hepatitis and cholestatic were reported with thiocolchicoside. Serious cases (for example fulminant hepatitis) were observed in patients that had taken NSAID or paracetamol at the same time. The patients have to be informed to report any sign of hepatic toxicity (see paragraph 4.8).

The use of thiocolchicoside is not recommended in children.

Each TIORELAX® tablet contains 33.84 mg of lactose. Patients affected with rare hereditary problems of intolerance to galactose, deficit of Lapp lactose, or malabsorption of glucose/galactose, should not take this medicine.

Thiocolchicoside may accelerate seizures, particularly in patients with epilepsy or in patients at risk for seizures (see section 4.8).

Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed.

The treatment must be discontinued in case of presence of diarrhea following oral administration.

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

Based on recent clinical experience, concomitant use of TIORELAX® with non-steroidal antiinflammatory agents, phenylbutazone, analgesics and preparations used in the treatment of neuritis, anabolic steroids, sedatives, barbiturates and succinylcholine is successful and safe.

Concomitant use of thiocolchicoside with other skeletal muscle relaxants is not recommended as they may increase the effect of each other. For the same reason, when used with another medicinal product that has an effect on smooth muscles, care should be taken and the patient should be observed, in case of the increased incidence of adverse effects.

Additional information on special populations

No interaction study has been performed for special populations.

Pediatric population:

No interaction study has been performed in pediatric populations.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: X

TIORELAX® is contraindicated during pregnancy (see section 4.3).

Women with childbearing potential / Contraception

Women with childbearing potential should use effective contraception during treatment.

Pregnancy

There are limited data on the use of thiocolchicoside in pregnant women.

Therefore, the potential hazards for the embryo and foetus are unknown.

Studies in animals have shown teratogenic effects (see section 5.3). . TIORELAX® is contraindicated during pregnancy and in women of childbearing potential not using contraception.

Lactation

Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated during breastfeeding (see section 4.3).

Fertility

In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is a risk factor for impairment of human fertility (see section 5.3). As a precautionary measure, use of the product at doses exceeding the recommended dose or long-term use should be avoided (see section 4.2).

4.7. Effects on ability to drive and use machines

No data are available on the ability to drive or use of machinery.

Clinical studies have concluded that thiocolchicoside has no effect on psychomotor performance. Since drowsiness is a common occurrence, this must be taken in account when driving or using machinery.

4.8. Undesirable effects

The adverse effects observed in clinical trials and associated with thiocolchicoside are listed below:

Adverse drug reactions are given according the following order of frequency: 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 ($< 1/10,000$); not known (cannot be estimated from the available data)

Immune system disorders

Uncommon: Pruritus Rare: Urticaria

Not known: angiodoema and anaphylactic shock after intramuscular administration.

Nervous system disorders

Common: Somnolence

Not known: vasovagal syncope (generally in the minutes following intramuscular administration), transient mental fog or excitation, convulsions

Cardiovascular system disorders

Rare: Hypotension

Gastrointestinal disorders

Common: Diarrhea (see section 4.4), gastralgia

Uncommon: Nausea, vomiting

Hepatobiliary disorders

Not known: Cytolytic and cholestatic hepatitis (see section 4.4).

Skin and subcutaneous tissue disorders

Uncommon: Allergic skin reaction

Reporting of suspected adverse reactions

Reporting any suspected adverse reactions of drugs is very important after the authorization. Reporting enables tracking the benefit/risk balance of the medicinal product. Health professionals should report any suspected adverse reaction 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

No specific symptom of overdose has been reported in patients treated with thiocolchicoside.

Treatment:

In case of overdosage it is recommended to get medical attention and implement symptomatic measures (see paragraph 5.3)

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Centrally acting myorelaxant

ATC Code: M03BX05

Thiocolchicoside is a semisynthetic sulphide derivative of colchicoside, showing muscle relaxant pharmacological activity.

In vitro thiocolchicoside binds solely with GABA-A and stricine-sensitive glycine receptors. From the moment that thiocolchicoside acts as an antagonist of the GABA-A receptors, its muscle relaxant effect may be exercised to a supraspinal level, through a regulatory mechanism even though the glycinergic mechanism of action cannot be excluded. The characteristics of interaction with the GABA-A receptors are qualitative and quantitative divided between thiocolchicoside and its main circulating metabolite, the derivative glucuronidated (see section 5.2)

In vivo the muscle relaxant properties of thiocolchicoside and its main metabolite have been shown in various predictive models of rat and rabbit. The lack of muscle relaxant effect of thiocolchicoside in spineless rat suggests a predominant supraspinal activity.

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

5.2. Pharmacokinetic properties

General properties:

Thiocolchicoside is a centrally acting myorelaxant and a white - yellow colored crystalline powder. TIORELAX® is a yellow, round, biconvex tablet, debossed “4” on one face and scored on the other face.

Absorption:

After oral administration, no thiocolchicoside is detected in plasma. Only two metabolites are observed:

The pharmacologically active metabolite SL18.0740 and an inactive metabolite SL59.0955. For both metabolites, maximum plasma concentrations occur 1hour after thiocolchicoside administration. After a single oral dose of 8 mg of thiocolchicoside the C_{max} and AUC of SL18.0740 are about 60 ng/mL and 130 ng.h/mL respectively. For SL59.0955 these values are much lower: C_{max} around 13 ng/mL and AUC ranging from 15.5 ng.h/mL (until 3h) to 39.7 ng.h/mL (until 24h).

Distribution:

In humans, thiocolchicoside is bound to serum proteins at a low level (13%) and this binding is independent of therapeutical thiocolchicoside concentration; serum albumin is mainly involved in serum protein binding. The apparent volume distribution and systemic clearance of thiocolchicosidine are about 43 L/h and 19 L/h, respectively.

Biotransformation

After oral administration, thiocolchicoside is first metabolized in the aglycon 3-demethylthiocolchicine or SL59.0955. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged thiocolchicoside by this route of administration. SL59.0955 is then glucuroconjugated into SL18.0740 which has equipotent pharmacological activity to thiocolchicoside and thus supports the pharmacological activity after oral

administration of thiocolchicoside. SL59.0955 is also demethylated into didemethyl-thiocolchicine.

Elimination:

After oral administration of radiolabelled thiocolchicoside, 79% of the dose is recovered in faeces and 20% in urine. No unchanged thiocolchicoside is excreted either in urine or feces. SL18.0740 and SL59.0955 are found in urine and feces while the didemethyl-thiocolchicine is only recovered in feces.

After oral administration of thiocolchicoside, the SL18.0740 metabolite is eliminated with an apparent $t_{1/2}$ ranging from 3.2 to 7 hours and the metabolite SL59.0955 has a $t_{1/2}$ averaging 0.8h.

5.3. Preclinical safety data

Acute toxicity:

At high doses, thiocolchicoside induced emesis in dog, diarrhoea in rat and convulsions in both rodents and non-rodents after acute administration by oral route.

Chronic toxicity:

Thiocolchicoside profile has been assessed *in vitro*, and *in vivo* following parenteral and oral administration.

Thiocolchicoside 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 ≤ 2 mg/kg/day in the rat and ≤ 2.5 mg/kg/day in non-human primate, and by the intramuscular route in the primate at repeated doses up to 0.5 mg/kg/day for 4 weeks.

At high doses, thiocolchicoside induced emesis in dog, diarrhoea in rat 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 intramuscular route.

Carcinogenicity:

The carcinogenic potential was not evaluated.

Genotoxicity:

Thiocolchicoside itself did not induce gene mutation in bacteria (Ames test), *in vitro* chromosomal damage (chromosome aberration test in human lymphocytes) and *in vivo* chromosomal damage (in vivo micronucleus in mouse bone marrow administered intraperitoneally).

The major glucuro-conjugated metabolite SL18.0740 did not induce gene mutation in bacteria (Ames test); however it induced *in vitro* chromosomal damage (*in vitro* micronucleus test on human lymphocytes) and in vivo chromosomal damage (*in vivo* micronucleus test in mouse bone marrow administered orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH centromere staining), suggesting aneugenic properties. The aneugenic effect of SL18.0740 was observed at concentrations in the *in vitro* test and at AUC plasma exposures in the in vivo test higher (more than 10 fold based on AUC) than those observed in human plasma at therapeutic doses. The aglycon metabolite (3-demethylthiocolchicine-SL59.0955) formed mainly after oral administration induced in vitro chromosomal damage (*in vitro* micronucleus test on human lymphocytes) and in vivo chromosomal damage (*in vivo* oral micronucleus test in rat bone

marrow administered orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH or CREST centromere staining), suggesting aneugenic properties. The aneugenic effect of SL59.0955 was observed at concentrations in the *in vitro* test and at exposures in the *in vivo* test close to those observed in human plasma at therapeutic doses of 8 mg twice daily per os.

Aneugenic effect in dividing cells may result in aneuploid cells. Aneuploidy is a modification in the number of chromosomes and loss of heterozygosity, which is recognized as a risk factor for teratogenicity, embryotoxicity/spontaneous abortion, impaired male fertility, when impacting germ cells and a potential risk factor for cancer when impacting somatic cells.

Teratogenicity:

In the rat, an oral dose of 12 mg/kg/day of thiocolchicoside caused major malformations along with foetotoxicity (retarded growth, embryo death, impairment of sex distribution rate). The dose without toxic effect was 3 mg/kg/day.

In the rabbit, thiocolchicoside showed maternotoxicity starting from 24 mg/kg/day. Furthermore, minor abnormalities have been observed (supernumerary ribs, retarded ossification).

Fertility impairment:

In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg/day, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is recognised as a risk factor for impairment of human fertility.

6. PHARMACEUTICAL PROPERTIES

6.1. List of Excipients

Microcrystalline cellulose
Lactose monohydrate (bovine)
Pregelatinized starch
Crospovidone
Colloidal silicon dioxide
Magnesium stearate

6.2. Incompatibilities

In the absence of the compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3. Shelf-life

36 months

6.4. Special precautions for storage

Store at room temperature below 25°C, in its packaging.

6.5. Nature and contents of container

In cardboard box containing 20 tablets in blister (white opaque PVC-Aluminum foil) packaging with the package leaflet.

6.6. Special precautions for disposal of waste materials derived from the medicinal product and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

217/ 2

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORIZATION

Date of first license: 25.09.2008
Date of renewal of the license: -----

10. DATE OF REVISION OF THE TEXT

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