# 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. See section 4.8 on how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

RELIEF® 4mg Capsule, hard
RELIEF® 4mg/2ml Solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION in active ingredients

Each hard capsule contains 4 mg Thiocolchicoside.
Each ampoule with 2 ml solution for injection contains 4 mg Thiocolchicoside
For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

- Capsule, hard
- Solution for injection

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

Posology:
- *For the oral formulation of 4 mg:* The recommended and maximum dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days.
- *For the oral and Intramuscular formulation:* Doses exceeding recommended doses or long-term use should be avoided (see Section 4.4).

*Paediatric population:*
RELIEF® should not be used in children and adolescents under 16 years of age because of safety concerns (see Section 5.3).
Method of administration:
Capsules, hard: Oral use
Solution for injection: Intramuscular use

### 4.3 Contraindications

Thiocolchicoside should not be used:

- In patients with hypersensitivity 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 flaccid paresis, muscular hypotonia
- In children

## 4.4 Special warnings and precautions for use

Cases of cytolytic and cholestatic hepatitis have been reported after thiocolchicoside became available in the market. In patients receiving concomitantly NSAIDs or paracetamol, serious cases have been reported (eg. Fulminant hepatitis). Patients should be instructed and report any sign of liver toxicity (see. Section 4.8 "Undesirable effects").
Thiocolchicoside may predispose to spasm, particularly in patients with epilepsy or patients at risk of epileptic seizures. (See Section 4.8 "Undesirable effects").

• *Capsules:* Due to the presence of lactose, patients with rare hereditary lactose intolerance problems, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
• *Capsules:* In case of diarrhea, treatment with thiocolchicoside must be discontinued.
• *Injectable solution:* Cases of fainting of vasomotor origin have been observed, therefore the patient should be monitored following the injection (see. Section 4.8. "Undesirable effects")

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, cancer, and impaired male fertility. 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).

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

## 4.5 Interactions with other medicinal products and other forms of interactions

It may develop synergistic effect if administered concomitantly with other myorelaxants or CNS sedative agents.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from 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).
The use of RELIEF® is contraindicated during pregnancy and in women of childbearing potential not using contraception (see section 4.3).
Breastfeeding 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 12mg/kg, 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 (see Section 5.3).

## 4.7 Effects on the ability to drive and use machines

There is no data available from clinical studies which suggest an effect on driving vehicles or operating machinery.

According to clinical studies thiocolchicoside does not affect the psychokinetic



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performance. However, since drowsiness can often occur, this should be taken into consideration when driving or using machines.

**4.8 Undesirable effects**

The following frequency scale by CIOMS is used: Very common (≥ 10%), common (≥ 1% to <10%), uncommon (≥ 0,1% to <1%), rare (≥ 0,01% to <0.1%), very rare (<0.01%), not known (cannot be evaluated from the available data).

***Immune system disorders***

Anaphylactic reactions including
Uncommon: Pruritus
Rare: Urticaria
Not known: Angioedema, anaphylactic shock following IM injection.

***Nervous system disorders***

Common: Drowsiness
Not known: Fainting of vasomotor origin usually occurring few minutes following IM injection (see. Section 4.4. "Special warnings and precautions for use"), spasms (see. Section 4.4. "Special warnings and precautions for use").

***Gastrointestinal disorders***

Common: Diarrhoea (see. Section 4.4. "Special warnings and precautions for use"), gastralgia,
Uncommon: Nausea, vomiting.

***Hepato-biliary disorders***

Not known: cytolytic and cholestatic hepatitis (see. Section 4.4. "Special warnings and precautions for use")

***Skin and subcutaneous tissue disorders***

Uncommon: Allergic skin reactions.

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to

- National Organization for Medicines, Mesogeion 284, GR-15662 Cholargos, Athens, www.eof.gr, Tel: + 30 213 2040380/337, Fax: + 30 210 6549585
- Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs Fax: + 357 22608649

**4.9 Overdose**

*Signs and symptoms*:
No specific overdose symptoms have been reported to patients under thiocolchicoside treatment. *Treatment*:
In case of overdose,, medical supervision general measures and symptomatic treatment are recommended. (see Section 5.3 "Preclinical safety data").

**5. PHARMACOLOGICAL PROPERTIES**

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: muscle relaxant, ATC code: M03B X05

Thiocolchicoside is a semi-synthetic sulfur derivative of colchicoside, a naturally occurring glucoside contained in the plant "meadow-saffron" with muscle relaxant activity but without the effect of curare.

It appears that thiocolchicoside acts as a selective antagonist of GABA and glycinergic receptors. This may explain its action on reflex contractions and contractions due to traumatic and rheumatologic disorders as well as spasms originating centrally.

Thiocolchicoside does not alter voluntary motility and does not act on the muscles of the respiratory system.

Thiocolchicoside does not affect the cardiovascular system.

## 5.2 Pharmacokinetic properties

Absorption

- After IM administration, thiocolchicoside Cmax occurs in 30 min and reaches values of 113 ng/mL after a 4 mg dose and 175 ng/mL after an 8 mg dose. The corresponding values of AUC are respectively 283 and 417 ng.h/mL.
The pharmacologically active metabolite SL18.0740 is also observed at lower concentrations with a Cmax of 11.7 ng/mL occurring 5 h post dose and an AUC of 83 ng.h/mL.
No data are available for the inactive metabolite SL59.0955.

- 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 Cmax and AUC of SL18.0740 are about 60 ng/mL and 130 ng.h/mL respectively. For SL59.0955 these values are much lower: Cmax around 13 ng/mL and AUC ranging from 15.5 ng.h/mL (until 3h) to 39.7 ng.h/mL (until 24h).

Distribution

The apparent volume of distribution of thiocolchicoside is estimated around 42.7 L after an IM administration of 8 mg. No data are available for both metabolites.

Biotransformation

After oral administration, thiocolchicoside is first metabolized in the aglycon 3-demethyltiocolchicine 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 IM administration the apparent t1/2 of thiocolchicoside is 1.5h and the plasma clearance 19.2 L/h.



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- After oral administration, total radioactivity is mainly excreted in feces (79%) while urinary excretion represents only 20%. 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 t1/2 ranging from 3.2 to 7 hours and the metabolite SL59.0955 has a t1/2 averaging 0.8h.

## 5.3 Preclinical safety data

Thiocolchicoside safety 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 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 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 IM route.

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 administred 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. The presence of the aglycon metabolite (3-demethylthiocolchicine-SL59.0955) after intramuscular administration has never been assessed, therefore its formation using this route of administration cannot be excluded.

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).

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.

The carcinogenic potential was not evaluated.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

***Capsules:***

Lactose monohydrate, Maize starch, Magnesium stearate/
*Composition of empty capsule No 2 (white-green)*
Titanium dioxide E 171, Quinoline yellow E 104, Indigo carmine E 132, Gelatine.

***Injectable solution:***

Sodium chloride, Water for injections.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months.

### 6.4 Special precautions for storage

Store at room temperature (15°C -25°C)..
Keep out of the reach of children.

### 6.5 Nature and contents of the container

***Capsules***:

Relief® caps are available in blister pack made of PVC/PVDC and aluminum foil. The product characteristics and lot number are printed on every blister that contains 10 capsules.
Each box contains 2 or 3 blisters, that is 20 or 30 capsules and one patient information leaflet..

***Injectable solution***:

Relief® Inj. Sol. is available in 2 ml transparent, glass ampoules. The product characteristics and lot number are printed on every ampoule. The ampoules are placed in a plastic case with 10 places. Each carton contains 1 plastic case with 10 ampoules and one patient information leaflet.

### 6.6 Precautions of use /handling

Any unused product or waste material should be disposed in accordance with local

requirements.

## 7. MARKETING AUTHORISATION HOLDER

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## 8. MARKETING AUTHORIZATION NUMBER

RELIEF® Capsule, hard: 92279/15/13-01-2016
RELIEF® Solution for injection: 92279/15/13-01-2016

Number of Special Authorization in Cyprus:
Capsule, hard: S00728
Solution for injection: S00730

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

Greece:
Date of first Authorisation: 02-10-2000
Date of Latest Renewal: 25-04-2011

Cyprus:
Date of first Authorisation: 08-09-2010
Date of Latest Renewal: 24-04-2013

## 10. DATE OF (PARTIAL) REVISION OF THE TEXT

10/2014

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