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 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

MAXTHIO 4 mg/2 ml Solution for I.M. Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Thiocolchicoside……4 mg

Excipient(s):
Sodium chloride…….....16.8 mg
Sodium citrate dihydrate……0.0056 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Light yellow coloured, clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the adjuvant treatment of painful muscle spasms in acute spinal pathology in adults and adolescents from 16 years onwards.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Adults:
The recommended and maximal dose is 4 mg every 12 hours (i.e. 8 mg per day).
The recommended duration of treatment with the solution for injection is 3-5 days. The treatment duration is limited to 5 consecutive days.

Doses exceeding recommended doses or long-term use should be avoided.

For preparation in physiotherapy sessions; the duration required to achieve muscle relaxant effect (30-40 minutes after I.M. injection) should be taken into consideration.

Method of administration
For intramuscular (I.M.) administration.

Additional information on special populations
Renal/Hepatic impairment
The safety and efficacy of MAXTHIO in patients with renal/hepatic impairment has not been investigated.

Pediatric population:
MAXTHIO 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 MAXTHIO in elderly patients has not been investigated.

4.3 Contraindications

It is contraindicated in:

- Flaccid-paralysis, muscular hypotonia,
- Patients with hypersensitivity to thiocolchicoside or to any of the excipients ,
- During the entire period of pregnancy and lactation,
- Children under 16 years of age,Women of childbearing potential not using contraception (see section 4.6).

4.4 Special warnings and precautions for use

Preclinical studies showed that one of thiocolchicoside 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/feto-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).

Cytolytic and cholestatic hepatitis have been reported with thiocolchicoside in post-marketing experience. Severe cases (e.g. fulminant hepatitis) have been reported in patients concomitantly administered with NSAID or paracetamol. Patients should be apprised of an immediate notification of liver toxicity's possible symptoms (see section 4.8).

Thiocolchicoside is not recommended for use in children.

Thiocolchicoside can precipitate seizures, particularly in patients with epilepsy or in patients predisposed to 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.

In case of diarrhea, the treatment with thiocolchicoside should be discontinued.

Cases of vasovagal syncope have been reported; therefore, patients should be monitored after injection (see section 4.8).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose; no sodium related side effect expected at this dose.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction has been reported. However; caution should be taken when it is used with other drugs of similar effect.

Additional information on special populations:
No interaction study has been conducted for special populations.

Pediatric population:
No interaction study has been conducted for pediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy category is X
MAXTHIO is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential/Contraception
There are no sufficient data on the use of thiocolchicoside in pregnant women.
Studies in animals have shown reproductive toxicity including teratogenic effects. The potential risk for human is unknown.
Women of child-bearing potential must use an effective method of contraception during treatment.

Pregnancy
Animal studies have shown reproductive toxicity (see section 5.3). There are insufficient clinical data to evaluate the safety of use during pregnancy. Therefore, potential harm to the embryo and fetus is unknown.
In conclusion, thiocolchicoside is contraindicated during pregnancy and in women of childbearing potential not using contraception (see section 4.3).

Breast-feeding
Since it passes into the mother's milk, MAXTHIO should not be used during breastfeeding (see section 4.3).

Reproductive ability / 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. The aneugenic effect is known to be a risk factor for impaired male fertility in humans (see section 4.4). As a precaution, overdose or prolonged use of the product should be avoided (see section 4.2).

4.7 Effects on ability to drive and use machines

There are no data available as to its effect on ability to drive and use machines.
Clinical studies have revealed that thiocolchicoside does not have any effect on psychomotor performance. However, as drowsiness may commonly occur, caution should be taken while driving and using machines.

4.8 Undesirable effects

Adverse effects that are related to the uptake of thiocolchicoside and observed in clinical studies are listed below:

Adverse drug reactions are defined in the below according to the following degree of frequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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
Unknown: Angioneurotic edema, anaphylactic shock following intramuscular injection

Nervous system disorders
Common: Somnolence
Not known: Vasovagal syncope occurring generally within a couple of minutes following intramuscular injection (see section 4.4), convulsions (see section 4.4).

Cardiovascular system disorders
Rare: Hypotension following intramuscular administration

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 suspected adverse reactions after authorization 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 the national reporting system.

4.9. Overdose

Symptoms:_A specific symptom of overdose has not been reported in patients treated with thiocolchicoside.

Treatment: In case of overdose, medical supervision and symptomatic precautions are recommended (see section 5.3).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Central acting myorelaxant
ATC Code: M03BX05

Thiocolchicoside is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. *In vitro,* thiocolchicoside only binds to GABA-A and strychnine-sensitive glycinergic receptors. Thiocolchicoside, acting as a GABA-A receptor antagonist, may exert its muscle relaxant effects via complex regulatory mechanisms at supraspinal level; however, its glycinergic mechanism of action cannot 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 section 5.2).

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.

5.2. Pharmacokinetic properties

Absorption:
After I.M. administration, thiocolchicoside C_{max} occur in 30 min and reach values of 113 ng/ml after a 4 mg dose and 175 ng/ml after a 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 C_{max} 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.

Distribution:
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 an I.M. administration of 8 mg, the apparent volume of distribution and systemic clearance of thiocolchicoside is estimated around 42.7 liter/hour and 19 liter/hour, respectively. No data are available for both metabolites.

Biotransformation:
After oral administration, thiocolchicoside is first metabolized in the aglycon 3-demethyltiocolchicine (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 metabolized 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 I.M. administration the apparent elimination half life ($t_{1/2}$) of thiocolchicoside is 1.5 h and the plasma clearance 19.2 L/h.

Linearity/Non-linearity:
After single-dose administration of 8 mg thiocolchicoside via intramuscular route, the mean area under the curve (AUC) reflecting the exposure of thiocolchicoside and its glucuronide metabolite to the active compounds is approximately 500 ng.hour/ml.

5.3 Preclinical safety data

Acute toxicity:
At high doses, thiocolchicoside induced emesis in dogs, diarrhea in rats 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 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, after acute oral administration, thiocolchicoside induced vomiting in dogs, diarrhea in rats, and convulsions in both rodents and non-rodents.

After repeated administration, thiocolchicoside is 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* intraperitoneal micronucleus test in mouse bone marrow).

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. 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.

Teratogenicity:
In the rats, an oral dose of 12 mg/kg/day of thiocolchicoside caused major malformations along with fetotoxicity (retarded growth, embryo death, impairment of sex distribution rate). The dose without toxic effect was 3 mg/kg/day. In the rabbits, thiocolchicoside showed maternotoxicity starting from 24 mg/kg/day. Furthermore, minor abnormalities have been observed (supernumerary ribs, retarded ossification).

Fertility disorders:
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 (see Genotoxicity), which is recognized as a risk factor for impairment of human fertility (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Sodium citrate dihydrate
Water for injections

6.2 Incompatibilities

Unknown.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

Colorless, 2 ml type I glass printed ampoule with ring.
Each cardboard box contains 6 ampoules.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece/İSTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

219/29

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 28.05.2009
Date of last renewal : 28.05.2014

10. REVISION DATE OF TEXT

11.12.2018