Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Muscurel
Thiocolchicoside

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 8 mg of thiocolchicoside.

Excipient(s) with known effect: lactose monohydrate 215.4 mg per capsule and carmoisine (E122) 0.033 mg per capsule.

For a full list of excipients, please see Section 6.1.

3. PHARMACEUTICAL FORM

Capsule, with a transparent body and dark purple head, containing a yellow granular powder.
Box of 10 capsules

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Add-on therapy for painful muscle contractures in acute spinal pathology in adults and adolescents 16 years of age and older.

4.2. Posology and mode of administration

4.2.1. Posology

The recommended and maximum dose is 8 mg every 12 hours (i.e. 16 mg daily). The length of treatment is limited to 7 consecutive days.

Doses higher than the recommended doses or long-term use should be avoided (see Section 4.4).

4.2.2. Paediatric population

Muscurel should not be used in children or adolescents less than 16 years of age because of safety concerns (see Section 5.3).

4.2.3. Method of administration

Oral use.

The capsules must be swallowed with a glass of water.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- Hypersensitivity to colchicine.
- Pregnancy and women of childbearing age who are not using contraceptives (see Section 4.6).
- Breast-feeding (see Section 4.6).

4.4. Special warning and precautions for use

- In patients with epilepsy or seizure risks, as thiocolchicoside may predispose to seizures, it is recommended to evaluate the risk-benefit ratio of thiocolchicoside and to increase clinical monitoring. Any occurrence of seizures requires discontinuation of the treatment.
- Some cases of liver conditions (such as cytolytic or cholestatic hepatitis) have been reported with thiocolchicoside during post-market use. Serious cases (fulminant hepatitis) have been reported in patients taking NSAIDs or paracetamol concomitantly. Patients must discontinue treatment and contact their physician if any signs or symptoms of hepatic conditions develop (see Section 4.8).
- In case of diarrhoea, reduce the posology. As an option, the capsules may be ingested with a gastric dressing.
- Preclinical studies have shown that one of thiocolcoside metabolites (SL59.0955) induced aneuploidy (i.e. an abnormal number of chromosomes in cells after cell division) at concentrations close to those observed in humans exposed to twice-daily oral doses of 8 mg (see Section 5.3). Aneuploidy is considered as a risk factor for teratogenesis, embryo/foetotoxicité, spontaneous miscarriage, and impairment of male fertility, as well as a potential risk factor for cancer. As a precautionary measure, any use of this product at doses higher than the recommended dose, or for long-term treatment, should be avoided (see Section

4.2). Patients are to be carefully informed of the potential risk of a possible pregnancy and efficient contraceptive measures to be followed.
- This medicine contains lactose monohydrate. Patients with an intolerance to galactose, total lactase deficiency, or glucose and galactose malabsorption syndrome (rare hereditary diseases) should not take this medicine.
- This medicine contains carmoisine which may cause allergic reactions.

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

4.5.1. General information

Based on clinical experimentation, thiocolchicoside is used successfully and safely in combination with nonsteroidal anti-inflammatory drugs, phenylbutazone, analgesics and preparations used for the treatment of neuritis, anabolic steroids, sedatives, barbiturates and succinylcholine.

It is not recommended to use thiocolchicoside concomitantly with other medicines which have a muscle-relaxing effect on the muscular-skeletal system, as these may increase one another's impact. For the same reason, when thiocolchicoside is used with another medicine which produces effects on the smooth muscles, one should beware of a possible increase in the incidence rate of side effects, and ensure that the patient is monitored.

4.5.2. Additional information on special populations

No study on interaction with special populations has been reported.

4.5.3. Paediatric population

No study on the paediatric population has been reported.

4.6. Fertility, pregnancy and lactation

4.6.1. Pregnancy

There is limited available data on the use of thiocolchicoside in pregnant women. As a result, the potential risks for the embryo and the foetus are unknown. Animal studies have shown teratogenic effects (see Section 5.3).

Muscurel is contra-indicated during pregnancy and in women of childbearing age who are not using contraceptives (see Section 4.3).

4.6.2. Lactation

As thiocolchicoside passes into breast milk, its use is contra-indicated during breast-feeding (see Section 4.3).

4.6.3. Fertility

In a toxicity study on fertility in rats, no impairment of fertility was observed at doses up to 12 mg/kg, which matches dose levels with no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different dose levels, which is a risk factor for impairment of fertility in males (see Section 5.3).

4.7. Effects on the ability to drive and use machines

Clinical studies have not demonstrated any psychomotor impairments related to thiocolchicoside. However, drowsiness may commonly occur; this should be considered in vehicle drivers and machine operators.

4.8. Undesirable effects

Adverse events are classified per frequency as follows: Very Common (≥1/10), Common (≥1/100 and <1/10), Uncommon (≥1/1000 and <1/100), Rare (≥1/10000 and <1/1000), Very Rare (<1/10000), not known (cannot be estimated from the available data).

Immune system disorders	
Rare:	Hypersensitivity reactions such as urticaria.
Frequency unknown:	Hypersensitivity reactions such as angioedema and, exceptionally, anaphylactic shock.
Frequency unknown:	Anaphylactic reactions.
Skin and subcutaneous tissue disorders	
Uncommon:	Skin reactions such as pruritus, erythema, maculopapular eruptions and, exceptionally, vesiculobullous eruptions.
Gastrointestinal disorders	
Common:	Diarrhoea (see Section 4.4), gastralgia.
Uncommon:	Nausea, vomiting.

Hepatobiliary disorders	
Frequency unknown:	Hepatic conditions (such as cytolytic or cholestatic hepatitis) (see Section 4.4).
Nervous system disorders	
Common:	Drowsiness.
Frequency unknown:	Seizure or relapsed attack in epileptic patients (see Section 4.4).

4.9. Overdose

Signs and symptoms
Digestive signs of the diarrhoea or vomiting type are possible.

Treatment
In case of an overdose, monitoring by a physician and symptomatic treatment are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: centrally acting myorelaxant. **ATC code:** M03BX05

Thiocolchicoside is a sulphur-containing, synthetic analogue of a natural colchicum glucoside which behaves pharmacologically as a muscle relaxant, both in humans and in animals. It eliminates, or substantially decreases, centrally originating muscle contracture: in spastic hypertonia, it reduces the muscle's passive resistance to stretching and decreases, or removes, the residual contracture. Its muscle-relaxing effect can also be observed on the visceral muscles: it has, in particular, been demonstrated on the uterus.

However, thiocolchicoside has no curariform effect, since it acts through the central nervous system rather than paralysing the muscle's motor plaque. The pharmacological mode of action of thiocolchicoside has been partially explained: research conducted in 2003 and 2007 has shown that its myorelaxant activity may be caused by an agonist action on the glycine receptors located primarily in the brain stem and the spinal cord. Thiocolchicoside does not, therefore, impair voluntary motility or cause paralysis, and thus is devoid of any respiratory risk.

Thiocolchicoside has no influence on the cardiovascular system.

Lastly, thiocolchicoside also acts as an antagonist of A-type GABA receptors (mainly located in the cerebral cortex), this pharmacological action being known to have convulsant or pro-convulsant properties.

5.2. Pharmacokinetic properties

Absorption
Following oral administration, thiocolchicoside is undetectable in plasma. Only two metabolites are observed: the pharmacologically active metabolite SL18.0740 and the inactive metabolite SL59.0955. For these two metabolites, the maximum plasma concentrations occur 1 hour after thiocolchicoside administration.

After a single oral dose of 8 mg of thiocolchicoside, the C_{max} and AUC for SL18.0740 are approximately 60 ng/ml and 130 ng.h/ml, respectively. For SL59.0955, these values are significantly lower: C_{max} approximately 13 ng/ml and AUC from 15.5 ng.h/ml (AUC calculated up to 3h) to 39.7ng.h/ml (AUC up to 24h).

After intramuscular (IM) administration, the maximum plasma concentration (C_{max}) for thiocolchicoside 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 AUC values (area under curve) are, respectively, 283 and 417 ng.h/ml.

The pharmacologically active metabolite SL18.0740 is also observed at lower concentrations with a C_{max} at 11.7 ng/ml occurring 5 hours following administration of thiocolchicoside and an AUC of 83ng.h/ml.
There are no data regarding the inactive metabolite SL59.0955.

Distribution
The apparent volume of distribution of thiocolchicoside is estimated to be approximately 42.7LI after an 8 mg intramuscular administration. There is no data regarding the two metabolites.

Biotransformation
Following oral administration, thiocolchicoside is initially metabolised to aglycone 3-demethyl thiocolchicine or SL59.0955. This step occurs mainly through intestinal

metabolism, which explains the absence of unmodified thiocolchicoside through this route of administration. SL59.0955 is then glucuro-conjugated into SL18.0740, which has a pharmacological activity equivalent to thiocolchicoside, and therefore contributes to the pharmacological activity following oral administration of thiocolchicoside. SL59.0955 is also demethylated into didemethyl-thiocolchicine.

Elimination
Following oral administration of radio-labelled thiocolchicoside, total radioactivity is mainly excreted in the faeces (79%), while urine excretion only represents 20%. Unmodified thiocolchicoside is not excreted in the urine or faeces. SL18.0740 and SL59.0955 are found in the urine and faeces, while didemethyl-thiocolchicine is only found in the faeces.
Following oral administration of thiocolchicoside, the SL18.0740 metabolite is eliminated with an apparent t1/2 ranging from 3.2 to 7 hours, and the SL59.0955 metabolite with a t1/2 of approximately 0.8 hours.

5.3. Preclinical safety data

The toxicology profile of thiocolchicoside has been evaluated in vitro, and in vivo following parenteral and oral administration.
Thiocolchicoside is well tolerated following repeated oral administration up to 6 months in rats and non-human primates at doses ≤2 mg/kg daily in rats and 2.5 mg/kg daily in non-human primates, and following repeated intramuscular administration for 4 weeks in primates at doses up to 0.5 mg/kg daily.
At higher doses, following a single oral administration, thiocolchicoside causes vomiting in dogs, diarrhoea in rats, and seizures in rodents and non-rodents.
Following repeated administration, thiocolchicoside caused gastro-intestinal disorders (enteritis, vomiting) when administered orally, and vomiting when administered intramuscularly.
Thiocolchicoside itself does not induce gene mutation in bacteria (Ames test), in vitro chromosomal aberration (chromosomal aberration test on human lymphocytes), or in vivo chromosomal aberration (in vivo micronucleus assay in mouse bone marrow following intraperitoneal administration).
The main glucuro-conjugated metabolite SL18.0740 does not induce gene mutation in bacteria (Ames test); it does, however, cause in vitro chromosomal aberrations (in vitro micronucleus assay on human lymphocytes) and in vivo chromosomal aberrations (in vivo micronucleus assay in mouse bone marrow following oral administration). The micronuclei resulted mainly from chromosome loss (presence

of centromere in the micronuclei revealed by centromere-specific FISH staining), suggesting aneugenic properties. The aneugenic effect of SL18.0740 was observed at concentrations (in the in vitro test) and plasma exposures (in the in vivo test) which were higher (over 10-fold, based on AUC) than those observed in human plasma at therapeutic doses.

The aglycone metabolite (3-demethyl-thiocolchicine, or SL59.0955), formed mainly following oral administration, does induce in vitro chromosomal aberrations (in vitro micronucleus assay on human lymphocytes) and in vivo chromosomal aberrations (in vivo micronucleus assay in rat bone marrow following oral administration). The micronuclei resulted mainly from chromosome loss (presence of centromere in the micronuclei revealed by centromere-specific FISH or CREST staining), suggesting aneugenic properties. The aneugenic effect of SL59.0955 was observed at concentrations (in the in vitro test) and exposures (in the in vivo test) close to those observed in human plasma at therapeutic doses of 8 mg administered twice daily per os. The aneugenic effect in dividing cells may result in aneuploid cells. Aneuploidy is a modification in the number of chromosomes and a loss of heterozygosis, which has been recognised as a risk factor for teratogenesis, embryotoxicity/spontaneous abortion, and impaired male fertility when impacting germ cells, and as a potential risk factor for cancer when impacting somatic cells. As the presence of the aglycone metabolite (3-demethyl-thiocolchicine, or SL59.0955) following intramuscular administration has never been evaluated, its formation through this route of administration cannot be ruled out.

In rats, a daily oral dose of 12 mg/kg of thiocolchicoside caused major malformations and foetotoxicité (delayed growth, embryo death, alteration of the sex distribution ratio). The dose level with no toxic effect was 3 mg/kg daily. In rabbits, thiocolchicoside showed maternal toxicity starting from 24 mg/kg daily. In addition, minor abnormalities were observed (supernumerary ribs, delayed ossification).

In a rat fertility toxicity study, no fertility impairment was observed at doses up to 12 mg/kg daily, i.e. at dose levels not inducing any clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at various dose levels, which is recognised as a risk factor for impairment of human fertility. The carcinogenic potential has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Maize Starch
Magnesium stearate

Capsule shell
Gelatine
Purified water
Sodium laurilsulfate (E487)
Titanium dioxide (E171)
Indigo carmine (E132)
Carmoisine (E122)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

Cardboard box with one transparent PVC/Al blister package of 10 capsules.

6.6. Special precautions for disposal and other handlings

No special requirements.
Any unused product or waste material should be disposed of in accordance with the regulations in force.

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Bilim Pharmaceuticals, GOSB 41480 Gebze, Kocaeli, Turkey.

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

June 2018.

11. DOSIMETRY (if applicable)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (if applicable)

Not applicable