SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MYOXOL 4 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Thiocolchicoside .....4.0 mg

For one capsule.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology

The recommended and maximum dose is 8 mg every 12 hours (i.e., 16 mg per day). The duration of treatment is limited to 7 consecutive days.
Doses higher than recommended or long-term use should be avoided (see section 4.4).

Pediatric population

MYOXOL should not be used in children and adolescents under the age of 16 years for safety reasons (see section 5.3).

Method of administration

Oral route.
Swallow the capsules with a glass of water.

4.3. Contraindications

This medication is contraindicated in the following cases:

- Hypersensitivity to the active substance, to colchicine or to any of the excipients listed in section 6.1.
- Pregnancy and women of childbearing age not using contraception (see section 4.6).
- Breastfeeding (see section 4.6).

4.4. Special warnings and precautions for use

In patients with epilepsy or at risk of seizures, it is recommended to assess the benefit-risk ratio of thiocolchicoside and to increase clinical monitoring. The occurrence of seizures requires discontinuation of treatment.

Cases of liver damage have been reported with thiocolchicoside since its marketing. Severe cases (fulminant hepatitis) have been reported in patients taking concomitant NSAIDs or paracetamol. Patients should stop treatment and contact their doctor if signs and symptoms of liver damage develop (see section 4.8).

Preclinical studies have shown that one of the metabolites of thiocolchicoside (SL59.0955) induces aneuploidy (an abnormal number of chromosomes in cells after cell division) at concentrations close to those observed in humans exposed to doses of 8 mg twice daily orally (section 5.3). Aneuploidy is considered a risk factor for teratogenesis, embryo / fetotoxicity , spontaneous abortion, and impaired fertility in humans, as well as a potential risk factor for cancer. As a precaution, use of the product at doses higher than the recommended dose or long-term use should be avoided (see section 4.2).

Patients should be carefully informed of the potential risk of a possible pregnancy and the effective contraceptive measures to follow.

In case of diarrhea, reduce the dosage. If necessary, take the capsules with a gastric protectant.

This medicine contains lactose. Its use is not recommended in patients with galactose intolerance, Lapp lactase deficiency , or glucose-galactose malabsorption syndrome (rare hereditary diseases).

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

Not applicable.

4.6. Pregnancy and breastfeeding

Pregnancy

Data on the use of thiocolchicoside in pregnant women are limited. Therefore, the potential risks to the embryo and fetus are unknown.

Animal studies have shown teratogenic effects (see section 5.3).

MYOXOL is contraindicated during pregnancy and in women of childbearing age not using contraception (see section 4.3).

Breastfeeding

Given that thiocolchicoside passes into breast milk, its use is contraindicated during breastfeeding (see section 4.3).

Fertility

In a rat toxicity study, no impairment of fertility was observed at doses up to 12 mg/kg, corresponding to dose levels that did not induce any clinical effect.
Thiocolchicoside and its metabolites exert aneugenic activity at various dose levels, which is a risk factor for impaired fertility in men (see section 5.3).

4.7. Effects on the ability to drive vehicles and use machinery

Clinical studies have not shown any psychomotor alterations related to thiocolchicoside .
However, some cases of drowsiness have been reported; this should be taken into account by vehicle drivers and machine operators.

4.8. Undesirable effects

The classification of adverse events according to their frequency is 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 not known: hypersensitivity reactions such as Quincke's edema and, exceptionally, anaphylactic shock.
- Frequency not known: anaphylactic reactions.

Skin and subcutaneous tissue disorders

- Uncommon: skin reactions such as itching, erythema, maculopapular rashes and, exceptionally, vesiculobullous rashes .

Gastrointestinal disorders

- Common: diarrhea (see section 4.4), stomach pain.
- Uncommon: nausea, vomiting.

Hepatobiliary disorders

- Frequency not known: liver damage (see section 4.4).

Disorders of the nervous system

- Common: drowsiness.
- Frequency not known: convulsions or recurrence of seizures in epileptic patients (see section 4.4).

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 report any adverse effects suspected unwanted substance via the FRILAB declaration form available under the tab Pharmacovigilance information from the website: www.frilab.ch

4.9. Overdose

Signs and symptoms

Digestive symptoms such as diarrhea or vomiting are possible.

Treatment

In case of overdose, medical monitoring and symptomatic treatment are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class : MYORELAXANT, ATC code: M03BX05 .
(M: Muscle and Skeleton)

Thiocolchicoside , a synthetic sulfur analog of a natural colchicum glucoside, acts pharmacologically as a muscle relaxant in both humans and animals. It suppresses or significantly reduces centrally originating contractures: in spastic hypertonia, it decreases the passive resistance of the muscle to stretching and reduces or eliminates residual contractures. Its muscle-relaxant action is also evident in visceral muscles: it has been demonstrated, in particular, in the uterus.

However, thiocolchicoside has no curarizing effect: it acts via the central nervous system, not by paralyzing the motor endplate. The pharmacological mechanism of action of thiocolchicoside is partially understood: recent studies (2003 and 2007) have shown that its muscle-relaxant activity results from an agonist action on glycinergic receptors located primarily in the brainstem and spinal cord. Therefore, it does not impair voluntary movement, does not cause paralysis, and thus avoids any respiratory risks.

Thiocolchicoside has no influence on the cardiovascular system .

Finally, thiocolchicoside also acts as an antagonist of GABAA type receptors (mainly located in the cerebral cortex), this pharmacological action being known to have convulsant or proconvulsant properties .

5.2. Pharmacokinetic properties

Absorption

After oral administration, thiocolchicoside is not detected in plasma. Only two metabolites are observed: the pharmacologically active metabolite SL18.0740 and the inactive metabolite SL59.0955.

For both of these metabolites, peak plasma concentrations occur 1 hour after thiocolchicoside administration . After a single 8 mg oral dose of thiocolchicoside , the Cmax and AUC of SL18.0740 are approximately 60 ng / mL and 130 ng·h / mL , respectively . For SL59.0955, these values are much lower: Cmax of approximately 13 ng / mL and AUC ranging from 15.5 ng·h / mL (AUC calculated up to 3 h) to 39.7 ng·h / mL (AUC up to 24 h).

Biotransformation

After oral administration, thiocolchicoside is first metabolized into the aglycone 3-desmethyl-thiocolchicine or SL59.0955. This step occurs mainly by intestinal metabolism, explaining the absence of unchanged thiocolchicoside circulating via this route of administration.

SL59.0955 is then glucuronidated to SL.18.0740, which has pharmacological activity equivalent to that of thiocolchicoside , and therefore contributes to the pharmacological activity following oral administration of thiocolchicoside . SL59.0955 is also demethylated to didemethyl-thiocolchicine .

Elimination

After oral administration of thiocolchicoside When radiolabeled , the total radioactivity is primarily excreted in the feces (79%), while urinary excretion accounts for only 20%. Unchanged thiocolchicoside is not excreted in the urine or feces. SL18.0740 and SL59.0955 are found in both urine and feces, whereas didemethylthiocolchicine is found only in feces.
After oral administration of thiocolchicoside , the metabolite SL18.0740 is eliminated with an apparent $t_{1/2}$ ranging from 3.2 to 7 hours, and the metabolite SL59.0955 with a $t_{1/2}$ of approximately 0.8 hours.
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5.3. Preclinical safety data

The toxicological profile of thiocolchicoside was evaluated in vitro, and in vivo after parenteral and oral administration.

Thiocolchicoside is well tolerated after repeated oral administration for up to 6 months in rats and non-human primates at doses less than or equal to 2 mg/kg / day in rats and 2.5 mg/kg/day in non-human primates, and after repeated intramuscular administration for 4 weeks in primates at doses up to 0.5 mg/kg/day.

At high doses, after a single oral administration, thiocolchicoside causes vomiting in dogs, diarrhea in rats, and convulsions in rodents and non-rodents.

After repeated administration, thiocolchicoside caused gastrointestinal disturbances (enteritis, vomiting) via the oral route and vomiting via the IM route.

Thiocolchicoside itself does not induce gene mutation in bacteria (Ames test), chromosomal aberration in vitro (chromosomal aberration test on human lymphocytes) or chromosomal aberration in vivo (in vivo micronucleus test on mouse bone marrow after intraperitoneal administration) .

The main glucuronide metabolite SL18.0740 does not induce gene mutations in bacteria (Ames test); however, it causes chromosomal aberrations in vitro (in vitro micronucleus test in human lymphocytes) and in vivo (in vivo micronucleus test in mouse bone marrow after oral administration). The micronuclei resulted primarily from chromosome loss

(presence of centromeres 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) higher (more than 10 times based on AUC) than those observed in human plasma at therapeutic doses.

The aglycone metabolite (3-desmethyl-thiocolchicine or SL59.0955), formed primarily after oral administration, induces chromosomal aberrations in vitro (in vitro nucleus test on human lymphocytes) and in vivo (in vivo micronucleus test on rat bone marrow after oral administration). The micronuclei resulted mainly from chromosome loss (presence of centromeres 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 twice daily orally. The aneugenic effect in dividing cells can lead to aneuploid cells. Aneuploidy is an alteration in chromosome number and a loss of heterozygosity, which is recognized as a risk factor for teratogenesis, embryotoxicity / spontaneous abortion, and impaired male fertility when it affects germ cells, and as a potential risk factor for cancer when it affects somatic cells. Since the presence of the aglycone metabolite (3- desmethyl-thiocolchicine or SL59.0955) after intramuscular administration has never been evaluated, its formation using this route of administration cannot be ruled out.

In rats, an oral dose of 12 mg/kg/day of thiocolchicoside resulted in major malformations and fetotoxicity (growth retardation, embryonic death, altered sex ratio). The no-observed-adverse-effect level (NOAEL) was 3 mg/kg/day.

In rabbits, thiocolchicoside showed maternal toxicity at doses of 24 mg/kg/day and above. In addition, minor abnormalities were observed (supernumerary ribs, delayed ossification).

In a rat fertility toxicity study, no impairment of fertility was observed at doses up to 12 mg/kg/day, which are doses that do not induce any clinical effects. Thiocolchicoside and its metabolites exhibit aneugenic activity at various dose levels, which is recognized as a risk factor for impaired human fertility.

The carcinogenic potential has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate , polyvinylpyrrolidone (PVP K-30), isopropyl alcohol and magnesium stearate.
Capsule shell composition: gelatin.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special storage precautions

Store at a temperature below 30°C and away from light.

6.5. Nature and contents of container

Box of 15 capsules in blister pack (PVC/Aluminium).

6.6. Special precautions for disposal and handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

7. HOLDER, OPERATOR AND MANUFACTURER

Owner and operator :
FRILAB SA
17, rue des Pierres du Niton
1207 Geneva
SWISS

Manufacturer :
MJ BIOPHARM PVT. LTD.
L-7 MIDC Industrial Area, Taloja
Dist. Raigad 410 208 Maharashtra
INDIA

8. DATE OF REVISION OF THE TEXT

August 2024

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I