SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Tiocolis, 8 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tiocolis, 8 mg:
One tablet contains 8 mg of thiocolchicoside (Thiocolchicoside).
Excipient with known effect: lactose monohydrate 85,4 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Round, biconvex yellow tablets.

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

Dosage
The recommended and maximal dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days.

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

Paediatric population
Tiocolis should not be used in children and adolescents under 16 years of age because of safety concerns (see section 5.3).

Method of administration
Oral use.
Tablets should be swallowed with a glass of water.

4.3 Contraindications

Tiocolis must not be used
- 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.

4.4 Special warnings and precautions for use

Caution should be used when thiocolchicoside is administered to patients with epilepsy or patients with increased risk of epileptic seizure.
In case of epileptic seizure occurrence the treatment should be withdrawn.

In case of diarrhoea, dose should be reduced.

If it is necessary, tablets can be used with antacids.

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).

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

The product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6 Fertility, pregnancy and lactation

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).

Tiocolis 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 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).

4.7 Effects on ability to drive and use machines

No data indicating that thiocolchicoside affects ability to drive and use machines.
Although individual cases of somnolence were observed. Therefore in patients planning to drive, perform potentially dangerous activities or use machines the reaction to this medicinal product should be considered.

4.8 Undesirable effects

Frequency of adverse reaction occurrence was established based on the following method:

– common (≥1/100 do <1/10);
– uncommon (≥1/1 000 do <1/100);
– rare (≥1/10 000 do <1/1 000);
– very rare (≤1/10 000);
– frequency unknown (cannot be estimated from the available data).

Immune system disorders
- Very rare: allergic reactions - urticaria, Quincke oedema
- Frequency unknown: anaphylactic shock

Skin and subcutaneous tissue disorders
- Rare: vesicular rash
- Very rare: pruritus, erythema, maculopapular rash

Gastrointestinal disorders
- Rare: abdominal pain, diarrhoea, nausea i vomiting

Nervous system disorders
- Very rare: somnolence
- Frequency unknown: seizures or seizure recurrence in epileptic patients

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 Pharmacovigilance Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Al. Jerozolimskie 181C
02-222 Warsaw
Tel.: + 48 22 49 21 301
Fax: + 48 22 49 21 309
Website: https://smz.ezdrowie.gov.pl
Adverse reactions can also be reported to marketing authorisation holder.

4.9 Overdose

Oversode symptoms

Possible gastrointestinal reactions like diarrhoea or vomiting.

Treatment

In case of overdose medical supervision and symptomatic treatment are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other centrally acting agents

ATC code: M03BX05

Pharmacodynamic properties of a sulphur analogue of the naturally occurring colchicine glucoside thiocolchicoside consists on muscle relaxation both in human and animals. Suppresses or significantly reduces induced centrally muscle contraction: in spastic increased muscle contraction it decreases passive muscle resistance during stretching and either lowers or removes the remaining tension. Thiocolchicoside acts also as a visceral muscle relaxant: especially proven for uteral muscles.

On the other hand thiocolchicoside doesn't show curarine effect cause it acts through central nervous system not via motor plate infestation.

Pharmacological thiocolchicoside mechanism of action is known partially: newest studies (2003 and 2007) show that muscle relaxation is resulting from glycine receptor agonism in brainstem and spinal cord. As a result thiocolchicoside does not interfere with involuntary motility, cause paralysis, thus it does not cause any risk of respiratory dysfunction.

Thiocolchicoside does not affect vascular system. Furthermore, thiocolchicoside acts as GABA receptor antagonist (mainly in brainstem), this action is attributed to pharmacological seizure or seizure-promoting properties.

5.2 Pharmacokinetic properties

Absorption

After intramuscular 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.

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

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

Metabolism

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 intramuscular administration the apparent $t_{1/2}$ of thiocolchicoside is 1.5h and the plasma clearance 19.2 L/h.
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 $t_{1/2}$ 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

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 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 intramuscular 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 can not 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

Lactose monohydrate
Cellulose microcrystalline type 101
Cellulose microcrystalline type 102
Povidone (Type K30)
Sillica colloidal anhydrous
Crosspovidone (Type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters in carton box.

Tiocolis, 8 mg: 14 tablets.

6.6. Special precautions for disposal and other handling

No special precautions.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Biofarm Sp. z o.o.
ul. Wałbrzyska 13
60-198 Poznań
Poland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT