For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated. Please read carefully before using a new pack

Thiocolchicoside Injection 4mg/2ml
MYORIL®

COMPOSITION

MYORIL® 4mg/2ml
Each 2ml ampoule contains:
Thiocolchicoside I.P. 4mg
Water for Injection I.P. q.s.

Myoril® is also available separately as Myoril Capsules (Thiocolchicoside Capsules IP 4mg/8mg).

THERAPEUTIC INDICATIONS
As an adjuvant treatment in painful spasm associated with degenerative vertebral disorders and vertebral static problem, torticollis, dorsal pain, low back pain, traumatological and neurological disorders.

DOSAGE AND ADMINISTRATION
Recommended dosage and duration of administration:

Intramuscular route: The recommended and maximal dose is 4 mg every 12 hours (i.e. 8 mg per day). The treatment duration is limited to 5 consecutive days.

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

SPECIAL POPULATIONS
Children
Thiocolchicoside is not recommended for use in children below the age of 16 years.

CONTRA-INDICATIONS
- Hypersensitivity to thiocolchicoside or to any excipients in the formulation.
- Pregnancy and lactation (see 'Pregnancy and Lactation')
- **In women of childbearing potential who are not using effective contraception**

WARNINGS
In preclinical studies, 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 Preclinical Safety Data). Aneuploidy is reported as a risk factor for teratogenicity, embryofoetotoxicity/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 Dosage).

Postmarketing cases of cytolytic and cholestatic hepatitis have been reported with thiocolchicoside. Severe cases (i.e. fulminant hepatitis) have been reported in patients concomitantly taking NSAIDs or paracetamol. Patients should be advised to report any sign of liver toxicity (see Adverse reactions).

Thiocolchicoside may precipitate seizures, especially in patients with epilepsy or those at risk for seizures (see Adverse reactions).

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

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

Cases of syncope vasovagal have been observed and therefore the patient should be monitored after the injection (see Adverse reactions).

INTERACTION WITH OTHER DRUGS AND OTHER FORMS OF INTERACTION
No known interaction has been reported.

PREGNANCY
Studies conducted in animals have shown reproductive toxicity including teratogenic effects (see Non-clinical Safety Data and Warnings).

There are insufficient clinical data to evaluate safety of use in pregnancy. Thus, the potential hazards for the embryo and fetus are unknown. In consequence, thiocolchicoside is contraindicated in pregnancy and women of childbearing potential who are not using effective contraception (see 'Contraindications').

LACTATION
Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated during breast feeding (see Contraindications)

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
There are no data available of the effect on driving vehicles and using machines. Clinical studies concluded that thiocolchicoside has no effect on the psychomotor performance. However, somnolence may occur commonly, this has to be taken into account when driving vehicles and operating machines.

ADVERSE REACTIONS
The following CIOMS frequency rating is used, for oral and IM :
Very common ≥10%; Common ≥1 and <10%; Uncommon ≥ 0.1 and <1%;
Rare ≥0.01 and <0.1%; Very rare <0.01%, Unknown (cannot be estimated from available data).

- *Immune system disorders*
  Anaphylactic reactions, such as
  Uncommon: pruritus,
  Rare: urticaria
  Unknown: angioneurotic oedema, anaplylactic shock following intramuscular injection

- *Nervous system disorders*

Common: somnolence,
Unknown: syncope vasovagal, usually occurring in the minutes following the intramuscular injection (see Precautions), convulsions (see Warnings).

- *Gastrointestinal disorders*
  Common: diarrhoea (see "Precautions"), gastralgia
  Uncommon: nausea, vomiting

- *Hepatobiliary disorders*
  Unknown: cytolytic and cholestatic hepatitis (see Warnings).

- *Skin and subcutaneous tissue disorders*
  Uncommon: allergic skin reaction.

OVERDOSAGE

Signs and Symptoms

No specific symptoms of overdose have been reported in patients treated with thiocolchicoside.

Management

Should overdosage occur, medical supervision and symptomatic measures are recommended (see 'Nonclinical Safety Data).

PHARMACOKINETIC

ABSORPTION

After IM administration, thiocolchicoside maximum plasma concentrations 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 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). After topical repeated applications, there is no quantifiable systemic exposure to thiocolchicoside.

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.

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 IM administration the apparent elimination half-life (t ½-) of thiocolchicoside is 1.5h and the plasma clearance 19.2 L/h.

After oral administration of radiolabelled thiocolchicoside, 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.

NON-CLINICAL SAFETY DATA

ANIMAL PHARMACOLOGY

Thiocolchicoside safety profile has been assessed *in vitro* and *in vivo* following parenteral and oral administration.

ACUTE TOXICITY

At higher doses, thiocolchicoside induced emesis in dog, diarrhea in rat and convulsions in both rodents and non-rodents after acute administration by oral route.

CHRONIC TOXICITY

Thiocolchicoside was well tolerated following oral administration for periods of upto 6 months in both the rat and the non-human primate when administered at repeated doses of less than or equal to 2mg/kg/day in the rat and less or equal to 2.5mg/kg/day in non-human primate, and by the intra muscular route in the primate at repeated doses upto 0.5mg/kg/day for 4 weeks. After repeated administration, thiocolchicoside induced gastro-intestinal disorders (enteritis, emesis) by oral route and emesis by i.m. 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 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 oral micronucleus test in mouse bone marrow). 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 times based on AUC) than those observed in human plasma at therapeutic doses

The aglycon metabolite (3-demethylthiocolchicine-SL59.0955) 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). 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, embryo-toxicity/spontaneous abortion, impaired male fertility, when impacting germ cells and cancer when impacting somatic cells

TERATOGENICITY.
In the rat, a dose of 12 mg/kg 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. In the rabbit, thiocolchicoside showed maternotoxicity starting from 24 mg/kg. Furthermore, minor abnormalities have been observed (supernumerary ribs, retarded ossification).

IMPAIRMENT OF 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 (see Genotoxicity), which is recognised as a risk factor for impairment of human male fertility (see Warnings).

LIST OF EXCIPIENTS
Sodium Chloride
Hydrochloric Acid
Water for Injection

INCOMPATIBILITIES
In the absence of compatibility studies, the solution for injection should not be mixed with other medicinal preparations.

SHELF LIFE
Please refer to the outer carton.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 25ºC. Protect from light. Do not freeze

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
None

Manufactured by:
Samrudh Pharmaceuticals Pvt. Ltd.*
Plot No. J-174, J-168, J-168/1, M.I.D.C,
Tarapur - 401 506, Boisar, District: Thane.
*under technical guidance of Sanofi Healthcare India Private Limited

Marketed by:
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