COLRIL
(Thiocolchicoside)

4 mg

Capsules.

COMPOSITION

The active ingredient of COLRIL is thiocolchicoside.
Each capsule contains:
Thiocolchicoside …….4 mg.

THERAPEUTIC INDICATIONS

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

DOSAGE AND ADMINISTRATION

Posology

The recommended and maximal dose for the oral form 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.

Paediatric population:
should not be used in children and adolescents under 16 years of age because of safety concerns.

CONTRAINDICATIONS

Thiocolchicoside must not be used

- in patients hypersensitive to the active substance or to any of the excipients

- during the entire pregnancy period - during lactation

- in women of childbearing potential not using contraception

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Preclinical studies showed that one of thiocolchicoside metabolites 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. 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.

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

Post marketing cases of cytolytic hepatitis and cholestatic were reported with thiocolchicoside. The serious cases (for example fulminant hepatitis) were observed in patients that had taken NSAID or paracetamol at the same time. The patients have to be informed to report any sign of hepatic toxicity. The use of thiocolchicoside is not recommended in children. Patients affected with rare hereditary problems of intolerance to galactose, deficit of Lapp lactose, or malabsorption of glucose/galactose, should not take this medicine. Thiocolchicoside may accelerate seizures particularly in patients with epilepsy or in patients at risk for seizures. Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed. The treatment must be discontinued in case of presence of diarrhoea following oral administration.

DRUG INTERACTIONS

Based on recent clinical experience, concomitant use of THIOCOLCHICOSIDE with non-steroidal anti-inflammatory agents, phenylbutazone, analgesics and preparations used in the treatment of neuritis, anabolic steroids, sedatives, barbiturates and succinylcholine is successful and safe.

Concomitant use of thiocolchicoside with other skeletal muscle relaxants is not recommended as they may increase the effect of each other. For the same reason, when used with another medicinal product that has an effect on smooth muscles, care should be taken and the patient should be observed, in case of the increased incidence of adverse effects

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Pregnancy category: X. Thiocolchicoside is contraindicated during pregnancy There are limited data on the use of thiocolchicoside in pregnant women. Therefore, the potential hazards for the embryo and fetus are unknown. Studies in animals have shown teratogenic effects. is contraindicated during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated during breastfeeding.

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.

EFFECTS ON ABILITY TO DRIVE

There is no data available on the effect on driving vehicles and using machines. Somnolence may occur commonly and that has to be taken into account when driving vehicles and operating machines.

ADVERSE DRUG REACTIONS

Very common (≥ 10%) and common (≥1 and <10%) adverse reactions are somnolence, diarrhoea, gastralgia.

Immune system disorders

Uncommon: Pruritus Rare: Urticaria Not known: Angioedema and anaphylactic shock after intramuscular administration.

Nervous system disorders

Common: Somnolence Not known: vasovagal syncope (generally in the minutes following intramuscular administration), transient mental fog or excitation, convulsions

Cardiovascular system disorders

Rare: Hypotension Gastrointestinal Disorders Common: Diarrhea, gastralgia Uncommon: Nausea, vomiting

Hepatobiliary disorders

Not known: Cytolytic and cholestatic hepatitis.

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 at pv@searlecompany.com

OVERDOSE

No specific symptom of overdose has been reported in patients treated with thiocolchicoside

Treatment:

In case of over dosage, it is recommended to get medical attention and implement symptomatic measures

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Centrally acting myorelaxant

ATC Code: M03BX05

Thiocolchicoside is a semisynthetic sulphide derivative of colchicoside, showing muscle relaxant pharmacological activity.

In vitro thiocolchicoside binds solely with GABA-A and stricine-sensitive glycine receptors. From the moment that thiocolchicoside acts as an antagonist of the GABA-A receptors, its muscle relaxant effect may be exercised to a supraspinal level, through a regulatory mechanism even though the glycinergic mechanism of action cannot be excluded. The characteristics of interaction with the GABA-A receptors are qualitative and quantitative divided between thiocolchicoside and its main circulating metabolite, the derivative glucuronidated. In vivo the muscle relaxant properties of thiocolchicoside and its main metabolite have been shown in various predictive models of rat and rabbit. The lack of muscle relaxant effect of thiocolchicoside in spineless rat suggests a predominant supraspinal activity. Moreover, in electroencephalographic studies, thiocolchicoside and its main metabolite were shown to be devoid of any sedative effect.

Pharmacokinetic properties

Absorption

After IM administration, thiocolchicoside Cmax 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)

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.

Biotransformation

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 t1/2 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 metabolites are 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.

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 IM 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 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. In the rat, 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 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 recognized as a risk factor for impairment of human fertility. The carcinogenic potential was not evaluated.

PRESENTATION

Colril 4 mg Capsules are available in ALU/PVC BLISTER STRIP 2x10 Capsules.

INSTRUCTIONS

- To be sold on prescription of a registered medical practitioner only.

- Protect from moisture, freezing, excessive heat and sunlight.

- Keep out of the reach of children.

REGISTRATION NUMBER

Colril 4 mg Capsules: 039261

Manufacturing Licence No :000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mfg. Searle Specs.

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

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