Date: 29th January 2014

COLTRAMYL (THIOCOLCHICOSIDE) FOR SYSTEMIC USE - IMPORTANT INFORMATION REGARDING INDICATIONS, TREATMENT REGIMEN, CONTRAINDICATIONS AND WARNINGS

Dear Healthcare Professional,

The MAH in agreement with the European Medicines Agency and the Medicines Authority would like to inform you of important restrictions regarding the use of thiocolchicoside-containing products for systemic use following the outcome of a review of new preclinical findings, which raised concerns about the activity of a thiocolchicoside metabolite on chromosomes.

Summary

New preclinical findings indicate a potential risk of genotoxicity from use of thiocolchicoside oral and intramuscular (IM) formulations.

- Systemic thiocolchicoside should only be used as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.
- Thiocolchicoside is not to be used for long-term treatment of chronic conditions.
- Doses should be restricted as follows and the recommended dose and duration should not be exceeded:
  - Oral forms: 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.
  - IM form: 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.
- Thiocolchicoside should not be used in pregnancy and lactation, nor in women of childbearing potential not using adequate contraception.

Further information

Thiocolchicoside is a muscle relaxant available as oral, injectable and topical formulations. In preclinical studies it has been shown that one of the thiocolchicoside metabolites (SL59.0955, also known as M2 or 3-demthylthiocolchicine) induced aneuploidy (i.e. unequal numbers of chromosomes in dividing cells) at concentrations close to those seen in humans who take the maximum recommended oral dose of 8 mg twice daily. Aneuploidy is reported as a risk factor for teratogenicity, embryofoetotoxicity/spontaneous abortion and impaired male fertility and a potential risk factor for cancer. The risk is greatest with long-term exposure.

Therefore, precautionary measures are to be taken in order to reduce the exposure to the metabolite SL59.0955 from systemic formulations. (Topical formulations do not produce significant systemic concentrations of the metabolite, and are not affected by these recommendations.)

Systemic thiocolchicoside should not be used for long-term treatment of chronic conditions, and treatment should be limited to 7 days for oral formulations, and to 5 days for injectable formulations. Moreover the dose should not exceed 8 mg every 12 hours for oral formulations and 4 mg every 12 hours for injectable formulations.

The benefits of systemic thiocolchicoside-containing formulations are considered to exceed their risks only when used in these dose schedules as adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards.

In order to minimise and manage the risk to the foetus, thiocolchicoside should not be used in pregnancy and lactation, nor in women of childbearing potential who are not using appropriate contraception.

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Extract from the Summary of Product Characteristics (SmPC) for thiocolchicoside-containing products for systemic use is annexed.

Call for reporting:
Healthcare professionals should report any adverse events suspected to be associated with the use Coltramyl to Sanofi Malta Ltd., St. Julian's Road, San Gwann SGN 2805. Tel: 21493022, fax: 21493024

Alternatively any suspected ADRs and medication errors can be reported to the Medicines Authority. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Company contact point
If you have any questions or require additional information, please call Medical Information Services at Sanofi Malta Ltd, St. Julian's Road, San Gwann SGN 2805. Tel: 21493022, fax 21493024

Yours Sincerely

Graziella Gravino B. Pharm (Hons)
Head of Regulatory Affairs & Pharmacovigilance
Sanofi Malta Ltd.

Annexes

Text of the revised local SmPC (with main changes highlighted)

Section 4.1: Therapeutic indications

Adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 15 years onwards.

Section 4.2: Posology and method of administration
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
Coltramyl should not be used in children and adolescents under 15 years of age because of safety concerns (see section 5.3).

Section 4.3: Contraindications
Thiocolchicoside 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

Section 4.4: Warnings and precautions for use

Thiocolchicoside should be administered with caution to epileptic patients or patients with a risk of convulsions.
In the case of diarrhoea, the dosage should be reduced.
If necessary, the tablets can be taken with an antacid.

Due to the presence of sucrose and lactose, the medicine is contraindicated in the case of congenital galactosemia, fructose intolerance, glucose-galactose malabsorption syndrome or lactase deficiency or sucrase-isomaltase deficiency.

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 reported as a risk factor for teratogenicity, embryo/foeto-toxicity, sp
ontaneous 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 section 4.2).
In case of diarrhoea the treatment with thiocolchicoside should be stopped.

Section 4.6: Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of thiocolchicoside in pregnant women. Therefore, the potential hazards for the embryo and foetus are unknown. Studies in animals have shown reproductive toxicity (see section 5.3).
Coltramyl 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 12mg/kg, 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 (see section 5.3).

Section 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 intra muscular 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 i.m. 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*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, embryotoxicity/ spontaneous abortion, impaired male fertility, when impacting germ cells and cancer when impacting somatic cells.

A teratogenic effect and perinatal toxicity was demonstrated at the higher doses tested. No evidence for teratogenic effects of thiocolchicoside was described at doses up to 3 mg/kg/day. 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 recognised as a risk factor for impairment of human fertility.

The carcinogenic potential was not evaluated.