Dear Healthcare Professional,

Sanofi 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.

In February 2013, the Italian Health Authority (AIFA) requested the European Medicines Agency’s (EMA’s) Committee for Human Medicinal Products (CHMP) to carry out a full assessment of the benefit-risk balance of systemic medicines containing thiocolchicoside.

The European Medicines Agency’s (EMA’s) Committee for Human Medicinal Products (CHMP) conducted the review concluding in its opinion on 21 November 2013, that the benefit-risk balance of thiocolchicoside containing medicinal products for systemic use as adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards remains favourable, subject to the restrictions, warnings, duration of use and contra-indicating systemic use in women of childbearing potential not using adequate contraception, during pregnancy or lactation and in children, additional pharmacovigilance activities and risk minimisation measures agreed.

Consequently, the following is recommended:

- 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 and injectable formulations in Pakistan. In preclinical studies it has been shown that one of the thiocolchicoside metabolites (SL59.0955, also known as M2 or 3-demethylthiocolchicine) 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, embryofetotoxicity/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.
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.

Packaging insert for thiocolchicoside-containing products for systemic use is attached.

**Call for reporting**
Please review carefully the revised enclosed product information and contact Sanofi if you have any additional questions.
Any adverse events experienced by your patients should be reported to Pakistan.Pharmacovigilance@sanofi.com

Yours sincerely,

Dr. Amanullah Khan
Medical Director

**Annexures:**

1- Text of the revised Package leaflet (with main changes highlighted in the following sections):
   (a) Indications  (b) Dosage & Administration  (c) Contraindications  (d) Warnings
   (e) Pregnancy & Lactation

2- Health Professional Guide

3- Patient Card