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European Medicines Agency recommends restricting use of thiocolchicoside by mouth or injection

Medicine only to be used at low doses for additional short-term relief of painful muscle contractures

On 21 November 2013 the European Medicines Agency's Committee on Human Medicinal Products (CHMP) recommended that the authorised uses for thiocolchicoside-containing medicines for use by mouth or injection should be restricted across the European Union (EU). These medicines are now recommended only as an add-on treatment for painful muscle contractures (permanent tightening of the muscle tissue) resulting from spinal conditions in adults and adolescents 16 years of age or older. In addition, the dose of thiocolchicoside by mouth or injection should be restricted.

Thiocolchicoside is a muscle relaxant that has been authorised by national procedures in several EU Member States[1] for use by mouth or injection into the muscles in the treatment of painful muscular disorders.

The review of thiocolchicoside was triggered by the Italian medicines regulatory agency, AIFA, following new experimental evidence which suggested that thiocolchicoside was broken down in the body into a metabolite called M2 or SL59.0955 that could damage dividing cells, resulting in aneuploidy (an abnormal number or arrangement of chromosomes). As a result AIFA asked the CHMP to examine the safety profile of this medicine and consider what regulatory action might be appropriate.

The CHMP reviewed the evidence, including the opinions of experts in the field of medicines safety, and concluded that aneuploidy could occur with M2 at levels not much greater than those seen after recommended doses of thiocolchicoside taken by mouth. Aneuploidy is a risk factor for harm to the developing fetus, reduced fertility in men and in theory could increase the risk of developing cancer. The CHMP therefore recommended measures to ensure thiocolchicoside-containing medicines are used as safely as possible. These include restricting the maximum dose and number of days of treatment when given by mouth or injection. Use is also contra-indicated in pregnancy and lactation or in women of childbearing potential not using contraception, as well as in children or for chronic (long-term) conditions. Preparations for local application to the skin, which do not produce substantial levels of M2 in the body, are not affected by this review.

The CHMP opinion was forwarded to the European Commission, which endorsed it and issued a final legally-binding decision, valid across the EU, on 17 January 2014.

[1] Czech Republic, France, Greece, Hungary, Italy, Malta, Portugal and Spain.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Information to patients

- Thiocolchicoside is a medicine used in some EU countries for conditions associated with muscle pain.
- New evidence has shown that thiocolchicoside is broken down in the body into a substance called M2, which in sufficient amounts can affect the genetic material of the cells. This results in an abnormal number or arrangement of chromosomes, which can reduce fertility in men and, if it happens during pregnancy, can harm the developing baby in the womb. In theory, long-term exposure might increase the risk of cancer although there is currently no evidence of this.
- In order to minimise the amount of M2 produced in the body, and therefore any associated risks, medicines containing thiocolchicoside are now only recommended for short-term use as an addition to other treatment for pain due to permanent tightening of the muscles where there are problems with the spine, in adults and teenagers from 16 years of age.
- Treatment should now only be given for 7 days by mouth or 5 days by injection into the muscle. Patients who are taking thiocolchicoside for a long-term condition should have their treatment reviewed by their doctor at the next scheduled appointment.
- Medicines containing thiocolchicoside must never be taken if you are pregnant or breast-feeding. Women who might become pregnant must use contraception when taking these medicines.
- Thiocolchicoside-containing medicines are also available for application to the skin but these do not produce the same levels of M2 in the body and are not thought to affect the genetic material of cells. These medicines are therefore not affected by these recommendations.
- Patients who have any questions should discuss them with their doctor or pharmacist.

Information to healthcare professionals

- Systemic thiocolchicoside is recommended only as adjuvant treatment for acute muscle contractures in spinal pathology, for adults and adolescents from 16 years of age.
- It is not recommended for longer-term treatment of chronic conditions.
- The maximum recommended oral dose is 8 mg every 12 hours; treatment duration should be no more than 7 consecutive days. When given intramuscularly, the maximum dose should be 4 mg every 12 hours, for up to 5 days.
- Medicines containing thiocolchicoside should not be used during pregnancy and lactation, nor in women of childbearing potential who are not taking appropriate contraceptive measures.
- Patients being treated with systemic thiocolchicoside should have their treatment reviewed at the next scheduled appointment, and appropriate alternative treatments should be considered.
- Pharmacists should refer any patients who present a repeat prescription to their treating physician.
- Prescribers will be sent a letter giving them further information on the restriction of indication of systemic thiocolchicoside. Educational materials for prescribers and patients will also be prepared.
- The current findings do not apply to topical preparations of thiocolchicoside.

The Committee's recommendations were based on a review of available data from pre-clinical and clinical studies, published literature and post-marketing experience, and consultations with an expert working party on medicines safety. Preclinical studies indicated that the thiocolchicoside metabolite 3-demethylthiocolchicine (M2, SL59.0955) may be associated with aneuploidy (abnormal chromosome number and loss of heterozygosity) in dividing cells, at levels of exposure not much greater than those achieved in the body with maximum recommended oral doses. Aneuploidy is an established risk factor for teratogenicity, embryotoxicity or spontaneous abortion, and impaired male fertility. In theory it also increases the risk of cancer, although any significantly increased cancer risk would in general be dependent on long-term exposure to the causative substance. Thiocolchicoside metabolites were not associated with mutagenicity (changes to genes) or clastogenicity (structural damage to chromosomes). The Committee concluded that in the light of current evidence the benefit-risk for the medicine remained positive provided appropriate risk-mitigating measures were taken, including restricting the maximum dose and duration of use and contra-indicating use during pregnancy and lactation and in children.

More about the medicine

Thiocolchicoside is used as a muscle relaxant in the treatment of painful muscular conditions. It is thought to act on receptors in the nervous system that are involved in the regulation of muscle function.

Thiocolchicoside is authorised through national procedures in the Czech Republic, France, Greece, Hungary, Italy, Malta, Portugal and Spain. It is available for use by mouth or by injection into the muscles. In some countries it is also available as preparations to be applied to the skin, but these latter preparations are not affected by this review.

More about the procedure

The review of systemic thiocolchicoside-containing medicines was triggered on 15 February 2013 at the request of Italy, under Article 31 of Directive 2001/83/EC. This followed new evidence from experimental studies carried out by a marketing authorisation holder which suggested an effect on chromosomes by a metabolite of thiocolchicoside. The Italian medicines regulatory authority therefore requested the CHMP to carry out a full assessment of the benefit-risk balance of systemic medicines containing thiocolchicoside, and issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the European Union.

The CHMP opinion was forwarded to the European Commission, which issued a final legally-binding decision, valid across the EU, on 17 January 2014.

Contact our press officers

Monika Benstetter or Martin Harvey

Tel. +44 (0)20 7418 8427

E-mail: press@ema.europa.eu