



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Tetrazepam-containing medicines suspended across the EU

On 24 April 2013, following the recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC), the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed by majority the PRAC recommendation to suspend the marketing authorisations of tetrazepam-containing medicines across the European Union (EU). The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national marketing authorisation procedures across the EU.

Tetrazepam, a medicine of the benzodiazepine class, is used in several EU Member States to treat painful contractures (such as in low back pain and neck pain) and spasticity (excessive stiffness of muscles).

The review of tetrazepam was triggered by the French National Agency for the Safety of Medicine and Health Products (ANSM), following reports of serious skin reactions with this medicine in France. Having assessed all available data on the risk of skin reactions, including post-marketing data in the EU and the published literature, the PRAC concluded that tetrazepam is associated with a low but increased risk of serious skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome) compared with other benzodiazepines. The Committee also noted that, in the light of the risks identified, the available data on the effectiveness of tetrazepam were not sufficiently robust to support its use in the authorised indications.

The CMDh agreed with the PRAC conclusion that the benefits of these medicines do not outweigh their risks, and adopted a final position that the marketing authorisations should be suspended throughout the EU. Because the CMDh took this position by majority it was sent to the European Commission, which endorsed it and adopted a legally binding decision on 29 May 2013.

The suspension of the marketing authorisations can be lifted if the companies that market these medicines provide data identifying a specific group of patients for whom the benefits of tetrazepam-containing medicines outweigh the risks.

Information to patients

- Tetrazepam is a muscle relaxant used in painful conditions such as low back pain and neck pain as well as spasticity (excessive stiffness of muscles).



- As a result of the risk of unpredictable, serious skin reactions identified, tetrazepam-containing medicines will no longer be available in the EU.
- If you are taking a tetrazepam-containing medicine, you should not suddenly stop taking tetrazepam without your doctor's advice. You should make an appointment with your treating doctor to discuss your treatment. Your doctor may also consider an appropriate alternative treatment for you.

Information to healthcare professionals

- In light of the unfavourable benefit-risk balance, doctors should review their patients' treatment at their next appointment, and may consider an appropriate alternative treatment.
- Pharmacists should refer patients on a new or repeat prescription for tetrazepam to their treating physician.

The CMDh position is based on the PRAC review of all available data on the risk of skin reactions with tetrazepam, including post-marketing data in the EU and the published literature, and the available information on efficacy in licensed indications:

- The review found that half of the reported reactions with tetrazepam are skin disorders, which are sometimes serious, life-threatening or fatal. Serious skin reactions include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. They are unpredictable and can occur at any stage during treatment, including after short-term treatment, and at recommended doses.
- In the pharmacovigilance database of the originator product, Myolastan, a total of 513 cutaneous (or allergic) reactions were identified. 65 cases of SJS and TEN were reported. Although the majority of cases occurred in patients taking concomitant medications, the causal link with tetrazepam was strong in a high number of cases.
- The risk of skin reaction is higher with tetrazepam than with other benzodiazepines. This is possibly explained by a structural difference between tetrazepam and other benzodiazepines (i.e. the substituted cyclohexenyl ring of tetrazepam).
- Regarding its efficacy, four studies showed no difference between tetrazepam and other active medicines when used for spasticity. The efficacy of tetrazepam for painful contractures is supported mainly by two small double-blind placebo-controlled clinical trials showing limited efficacy.

In view of the serious, potentially fatal, skin reactions and the limited efficacy of tetrazepam, the benefit-risk balance of tetrazepam-containing medicines is considered no longer favourable.

More about the medicine

Tetrazepam belongs to a group of medicines called benzodiazepines. It is taken by mouth to treat painful contractures (sustained shortening of muscle tissue), and spasticity (excessive stiffness of muscles).

Tetrazepam-containing medicines have been approved since the 1960s via national procedures in several EU Member States (Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Latvia, Lithuania, Luxembourg, Poland, Romania, Slovakia and Spain), and are available on prescription under various trade names, including Epsipam, Miozepam, Musapam, Musaril, Myolastan, Myopam, Panos,

Relaxam, Spasmorelax, Tetra-saar, Tetramdura and Tetraratio. The full list is available in Annex I on the EMA website, under the 'All documents' tab.

Benzodiazepines work by attaching to certain receptors in the brain, thereby increasing the activity of a substance called gamma-amino butyric acid (GABA). GABA decreases the excitability of many brain cells. By increasing GABA activity, benzodiazepines have a calming effect on various functions of the brain. In particular, tetrazepam is used for its muscle relaxant effects.

More about the procedure

The review of tetrazepam-containing medicines was initiated in January 2013 at the request of France, under Article 107i of Directive 2001/83/EC, also known as the urgent Union procedure.

The review was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. As tetrazepam-containing medicines are all authorised nationally, the PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by majority vote, the CMDh position was sent to the European Commission, which endorsed it and adopted an EU-wide legally binding decision.

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