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PRAC recommends suspension of tetrazepam-containing medicines

Recommendation by PRAC to be considered by CMDh for final position

During its April 2013 meeting, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that, following reports of rare but serious and sometimes life-threatening skin reactions, the benefits of tetrazepam-containing medicines no longer outweigh their risks and these medicines should be suspended across the European Union (EU).

The PRAC recommendation will be considered by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)[1], which will take a final position. The final position is expected at the next CMDh meeting of 22 to 24 April 2013.

Why are tetrazepam-containing medicines being reviewed?

Following reports of serious skin reactions in France, the French National Agency for the Safety of Medicine and Health Products (ASNM) performed a review of data on all side effects with these medicines, especially skin reactions, recorded in the French national pharmacovigilance database. The review showed that side effects affecting the skin occurred at a higher rate in comparison with other benzodiazepines (medicines of the same class as tetrazepam). In addition, some reported skin reactions were very serious, including cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.

Given the seriousness of the skin reactions reported, the French medicines agency asked the PRAC to urgently review the use of tetrazepam-containing medicines in all indications.

What are the PRAC conclusions?

The PRAC assessed all available data on the risk of skin reactions with tetrazepam based on post-marketing data in Europe and the published literature. Stakeholders (healthcare professionals, patients and the general public) were also able to submit relevant information to support the assessment. The PRAC concluded that tetrazepam is associated with a low but increased risk of serious skin reactions compared with other benzodiazepines. The Committee also noted that in the light of the risks identified

[1] The CMDh is a medicines regulatory body representing the EU Member States.

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the available data on its effectiveness were not sufficiently robust to support its use in the authorised indications: treatment of painful muscle contractures (such as in low back pain and neck pain) and spasticity (excessive stiffness of muscles). The PRAC considered that measures had not been identified to sufficiently reduce the risk of serious skin reactions with tetrazepam-containing medicines given the uncertainties about the benefits. Therefore, the Committee concluded that the benefit-risk balance for these medicines is negative, and recommended that the marketing authorisations be suspended throughout the EU. It recommended that, for the suspension to be lifted, the companies that market these medicines should provide data identifying a specific group of patients for whom the benefits of tetrazepam-containing medicines outweigh the risks.

What will happen next?

The PRAC recommendation will be considered by the CMDh at its meeting of 22 to 24 April 2013. The CMDh will adopt a final position on whether the marketing authorisations for tetrazepam-containing medicines should be maintained, changed, suspended or withdrawn across the EU. The final CMDh position, together with full advice for patients and healthcare professionals, will be made public.

Patients and healthcare professionals should note that tetrazepam-containing medicines are not yet suspended and a final decision is still pending. Healthcare professionals should be aware about the risk of serious skin reactions. Once the procedure is finalised, healthcare professionals in the EU countries where tetrazepam is marketed will receive a letter with detailed information on the appropriate actions to be taken. Patients who have any questions should speak to their doctor.

More about the medicine

Tetrazepam belongs to a group of medicines called benzodiazepines. It is taken by mouth to treat painful muscle 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 such as Myolastan and as generics.

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 has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As tetrazepam-containing medicines are all authorised nationally, the PRAC recommendation will now be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a medicines regulatory body representing the EU Member States.

If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.