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Questions and answers on the review of tolperisone-containing medicines

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

On 21 June 2012, the European Medicines Agency completed a review of the safety and effectiveness of tolperisone. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of tolperisone-containing medicines given orally (by mouth) continue to outweigh their risks, but that their use should be restricted to the treatment of adults with post-stroke spasticity (stiffness). The Committee also recommended that the marketing authorisations for tolperisone-containing medicines given by injection should be revoked throughout the European Union (EU).

After re-examination, the Committee confirmed these recommendations on 18 October 2012.

What is tolperisone?

Tolperisone is a muscle relaxant. Tolperisone-containing medicines have been authorised in several countries in the EU since the 1960s for the treatment of muscle spasms (involuntary contractions) and spasticity caused by different conditions. These include neurological diseases (related to the brain or nerves, such as multiple sclerosis), locomotor diseases (related to the spine and large joints such as the hip), vascular diseases (related to the blood vessels), rehabilitation following surgery, and Little's disease (also known as cerebral palsy, a rare disease where there is damage to parts of the brain that control movement).

The exact way tolperisone works is not known, but it is thought to act in the brain and spinal cord to reduce the nerve impulses that make the muscles contract and become rigid. By reducing these impulses, tolperisone is believed to reduce muscle contraction, helping to relieve the stiffness.

Medicines containing tolperisone are available as tablets and/or solution for injection in Bulgaria, Cyprus, Czech Republic, Germany, Hungary, Latvia, Lithuania, Poland, Romania and Slovakia, under various trade names.



Why were tolperisone-containing medicines reviewed?

As tolperisone-containing medicines have been developed by different companies and have been authorised through national procedures in the EU Member States, they are used to treat different conditions in different countries. In Germany, several indications approved in other countries were not authorised because the German medicines agency considered that tolperisone's effectiveness had not been proven in those indications. In addition, numerous reports of hypersensitivity (allergic) reactions to tolperisone had been reported post marketing in Germany. Consequently, the German medicines agency considered that a full assessment of the benefit-risk balance of tolperisone should be carried out in all approved indications. On 15 July 2011, it asked the CHMP to issue an opinion on whether the marketing authorisations for tolperisone-containing products should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed data on the effectiveness of oral and injectable tolperisone in the different indications, including data from published clinical studies and analyses of various studies provided by the companies that market these medicines. The Committee also reviewed the available post-marketing data on spontaneous reports of side effects.

What are the conclusions of the CHMP?

The CHMP noted that most of the studies with oral tolperisone, performed in the 1960s and 1970s, were of a lower standard than that expected today. The available data to support the use of tolperisone-containing medicines in locomotor diseases, vascular diseases, rehabilitation following surgery and Little's disease are limited and not convincing. Only in the treatment of spasticity caused by neurological diseases was a study considered to be of acceptable quality, showing a moderate improvement of 32% in spasticity with oral tolperisone, compared with a 14% improvement in the placebo (a dummy treatment) group. However, the study only included adults with post-stroke spasticity.

Regarding the safety of tolperisone, the CHMP noted that more than half of the spontaneous reports of side effects with tolperisone were hypersensitivity reactions, while only a small number of hypersensitivity reports had been observed during the clinical trials that supported tolperisone's marketing authorisation. The Committee therefore recommended that the product information should be updated to reflect this risk and include a warning on the signs of hypersensitivity.

Therefore, based on the evaluation of the currently available data and considering that the risk of hypersensitivity reactions is more significant than previously identified, the CHMP concluded that the benefits of oral tolperisone-containing medicines continue to outweigh its risks only when used in the treatment of post-stroke spasticity in adults. In addition, since extremely limited data are available to support the safety and dosing recommendations of injectable tolperisone, the CHMP concluded that the benefits of this formulation do not outweigh the identified risks, and that the marketing authorisations for tolperisone-containing medicines given by injection should be revoked.

The CHMP confirmed the above conclusions after re-examining its opinion. The full changes made to the information to doctors and patients are detailed [here](#).

What are the recommendations for patients?

- Patients should be aware that the benefits of oral tolperisone continue to outweigh its risks only for the treatment of post-stroke spasticity in adults.

- Patients currently using tolperisone for any other indication or using injectable tolperisone should speak to their doctor at their next routine appointment so they can switch to an appropriate alternative treatment.
- Patients should note that symptoms of hypersensitivity can include flushing, rash, severe itching of the skin (with raised lumps), wheezing, difficulty breathing, difficulty in swallowing, fast heartbeat, low blood pressure and fast decrease in blood pressure. Patients should stop taking tolperisone and inform their doctor if they experience any of these symptoms.
- Patients who have any questions should speak to their doctor or pharmacist.

What are the recommendations for prescribers?

- Prescribers are advised that the indication for oral tolperisone has been restricted to the treatment of post-stroke spasticity in adults. Doctors should stop prescribing tolperisone for any other indication.
- Prescribers are advised that injectable tolperisone should no longer be used in the EU.
- Patients should be informed of the possibility of hypersensitivity reactions during treatment with tolperisone. If symptoms of hypersensitivity occur, treatment should be stopped immediately.

The European Commission issued a decision on this opinion on 21 January 2013.