



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 March 2014
EMA/162540/2014

CMDh endorses recommendations to restrict the use of diacerein-containing medicines

Restrictions intended to limit risks of severe diarrhoea and effects on the liver

On 19 March 2014, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)¹ endorsed recommendations to restrict the use of diacerein-containing medicines in order to manage the risks of severe diarrhoea and effects on the liver.

Due to the risks associated with severe diarrhoea, diacerein is no longer recommended in patients aged 65 years and above. It is also advised that patients start treatment on half the normal dose (i.e. 50 mg daily instead of 100 mg) and should stop taking diacerein if diarrhoea occurs.

In addition, diacerein-containing medicines must now not be used in any patient with liver disease or a history of liver disease, and doctors should be monitoring their patients for early signs of liver problems.

Doctors should also note that, based on available data, the use of diacerein is to be limited to treating symptoms of osteoarthritis affecting the hip or knee. Treatment should only be started by doctors experienced in treating osteoarthritis.

These recommendations are based on the review of the benefits and risks of diacerein conducted by the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) and follow concerns raised by the French medicines agency (ANSM) about diacerein's gastro-intestinal and liver effects. The CMDh has endorsed the PRAC's final recommendations to address these concerns and ensure that diacerein's benefits continue to outweigh its known risks.

As the CMDh position on diacerein was adopted by majority vote, it will now be sent to the European Commission for a final legally binding decision valid throughout the European Union (EU).

Information to patients

Diacerein is a medicine used to treat joint diseases such as osteoarthritis (swelling and pain in the joints). Following an EU-wide review of diacerein, its use has been restricted in order to minimise the risks of severe diarrhoea and liver problems.

¹ The CMDh is a medicines regulatory body representing the European Union (EU) Member States



Patients are advised of the following:

- Diacerein should only be used for treating symptoms of osteoarthritis affecting the hip or knee.
- If you have diarrhoea while taking diacerein, stop taking your medicine and contact your doctor to discuss which other treatments you can take.
- If you are taking diacerein and you are 65 years or above, contact your doctor to discuss your treatment.
- You should not take diacerein if you have or have had liver problems. Your doctor will monitor your liver function on a regular basis and advise about the symptoms of liver problems (such as pruritus (itching) and jaundice). Contact your doctor if you have symptoms of liver problems.
- If you have any questions about your treatment, please contact your doctor or pharmacist.

Information to healthcare professionals

- Due to the risks associated with severe diarrhoea:
 - it is advisable to start treatment with half the normal dose (i.e. 50 mg per day) for the first 2 to 4 weeks, after which the recommended dose is 50 mg twice a day.
 - treatment should be stopped if diarrhoea occurs.
 - diacerein is not recommended in patients aged 65 years or above.
- Diacerein must not be used in any patient with liver disease or a history of liver disease. Doctors should be monitoring their patients for early signs of liver problems and advising them how to recognise early symptoms.
- Diacerein should only be used to treat symptoms of osteoarthritis of the hip or knee and it is not recommended for rapidly progressive hip osteoarthritis.
- Treatment should only be started by doctors experienced in treating osteoarthritis.

The recommendations are based on a review of available data on the efficacy and safety of diacerein. Efficacy in the symptomatic treatment of osteoarthritis of the hip or knee was shown in published studies where diacerein was superior to placebo in relieving pain¹⁻⁵. The first beneficial effects of diacerein in these studies were seen after 2 to 4 weeks of continuous use.

With regard to safety, loose stools or diarrhoea were the most frequently reported adverse events in clinical studies with diacerein at a dose of 100 mg per day. The proportion of patients with diarrhoea in clinical trials ranged from 0% to 54.4%. In the majority of cases diacerein-induced diarrhoea started in the first weeks of treatment.

Elevated serum liver enzymes and cases of symptomatic acute hepatic injury have been reported in the post-marketing phase with diacerein. In clinical studies, around 0.5% of patients on diacerein had some kind of liver reaction, with most cases being mild, reversible increases in serum transaminases. The proportion of patients who develop drug-induced liver injury following treatment with diacerein is estimated to be 0.03%.

References

1. Lequesne M, Berdah L, Gérentes I. Efficacy and Safety of Diacerein for the treatment of Knee and Hip Osteoarthritis [Efficacité et tolérance de la diacérhéine dans le traitement de la gonarthrose et de la coxarthrose]. *La Revue du Praticien* 1998;48:S31-S35
2. Pavelka K, Trc T, Karpas K, Vitek P, Sedlacková M, Vlasáková V, Böhmová J, Rovenský J. The Efficacy and Safety of Diacerein in the Treatment of Painful Osteoarthritis of the Knee. *Arthritis & Rheumatism* 2007;56:4055-4064.
3. Singh K, Sharma R, Rai J. Diacerein as adjuvant to diclofenac sodium in osteoarthritis knee. *International Journal of Rheumatic Diseases* 2012;15(1):69-77.
4. Pelletier JP, Yaron M, Haraoui B, Cohen P, Nahir M A, Choquette D, et al. Efficacy and Safety of Diacerein in Osteoarthritis of the Knee. *Arthritis and Rheumatism* 2000;43(10):2339-2348.
5. Nguyen M, Dougados M, Berdah L, Amor B. Diacerein in the treatment of osteoarthritis of the hip. *Arthritis Rheum.* 1994 Apr;37(4):529-36.

More about the medicine

Diacerein is a slow-acting medicine of the class 'anthraquinones' used to treat joint diseases such as osteoarthritis (swelling and pain in the joints). It works by blocking the actions of interleukin-1 beta, a protein involved in the inflammation and destruction of cartilage that play a role in the development of symptoms of degenerative joint diseases such as osteoarthritis.

Diacerein-containing medicines are taken by mouth and are currently authorised in the following EU Member States: Austria, Czech Republic, France, Greece, Italy, Portugal, Slovakia and Spain.

More about the procedure

The review of diacerein-containing medicines was initiated on 29 November 2012 at the request of the French medicines agency under Article 31 of Directive 2001/83/EC.

The review of diacerein was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). In November 2013, the PRAC initially recommended the suspension of the marketing authorisations for diacerein-containing medicines. However, following re-examination, the PRAC considered additional proposals to manage diacerein's risks and was satisfied that with new restrictions diacerein's benefits would outweigh its risks.

The PRAC's final recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which endorsed the recommendations and adopted a position by majority vote.

The CMDh position will now be sent to the European Commission for an EU-wide legally binding decision.

Contact our press officers

Monika Benstetter or Martin Harvey

Tel. +44 (0)20 7418 8427

E-mail: press@ema.europa.eu