

**Annex II**  
**Scientific conclusions**

## Scientific conclusions

The CMDh, having considered the revised final PRAC recommendation dated 10 July 2014 with regards to diacerein containing medicinal products, agrees with the recommendation therein as stated below:

### **Overall summary of the scientific evaluation of diacerein containing medicinal products** (see Annex I)

Diacerein is a symptomatic slow acting drug in osteoarthritis (SYSADOA). Even though its mechanism of action is not completely known, it differs from non-steroidal anti-inflammatory drugs (NSAIDs) as it does not inhibit prostaglandin synthesis nor affect its levels. Diacerein and its active metabolite, rhein, are anthranquinone derivatives. It is thought that diacerein works by blocking/reducing the actions of interleukin-1 $\beta$ , a protein involved in the process of articular cartilage destruction and synovial inflammation (Yaron M *et al.*, 1999; Alvarez Soria *et al.*, 2008; Legendre F *et al.*, 2009).

Diacerein was mainly indicated as an oral treatment for osteoarthritis (OA), a chronic joint degenerative disease with a high prevalence in the ageing population. Pain and functional disability of the affected joints are the main manifestations of osteoarthritis. The correct diagnosis includes both clinical and radiological criteria. In general, treatment includes non-pharmacological therapies such as weight control, physical therapy, exercise, patient education as well as pharmacological intervention. There is no consensus on the role of SYSADOA in the pharmacological treatment of OA. In general its place in therapy is considered supplementary to the analgesics and anti-inflammatory drugs.

In 2012, the French national competent authority (Agence nationale de sécurité du médicament et des produits de santé, ANSM) initiated a review of the benefit-risk of diacerein containing medicinal products that underlined the occurrence of very frequent digestive disorders, cases of hepatitis and serious skin reactions in patients treated with diacerein. In addition, and according to the clinical trials and bibliographical data, the efficacy appeared weak in the symptomatic treatment of osteoarthritis with low impact on pain and functional symptoms and with no demonstration of a decrease of NSAIDs intake in the population treated with diacerein.

In view of the above, the ANSM requested the PRAC to give a recommendation on the balance of benefits and risks of diacerein containing medicinal products in the authorised indications and whether their marketing authorisations should be maintained, varied, suspended or withdrawn.

#### *Efficacy issues*

As part of this referral procedure, the PRAC reviewed all available data on the efficacy of diacerein containing medicinal products.

The effects of diacerein on pain and physical functioning of the joints have been evaluated in a number of studies as primary endpoints. The structure-modifying effects of diacerein have also been assessed in few studies as well as its NSAIDs sparing effect (secondary endpoint).

Double blind placebo controlled clinical trials performed during the last 20 years showed heterogeneous results, which may be explained by the usual high placebo effect in this kind of indications. Overall, studies showed a modest but statistically significant effect on pain and physical functioning. However, although double blind was an intended methodological feature of the clinical trials performed with diacerein, it was considered doubtful that blinding was achieved in practice, considering the very apparent effects (urine coloration, diarrhoea) produced by diacerein. This point was not addressed in any of the trials. In addition, the missing data and their handling were considered problematic from a statistical point of view.

The evidence obtained from different meta-analysis of the clinical trials performed with diacerein showed a small beneficial effect of diacerein in the treatment of OA of the knee and hip with different criteria for the inclusion of the clinical trials in the meta-analyses. However, the quality of the studies was heterogeneous and publication bias could not be excluded since only published trials and non-published trials sponsored by the companies were included in the systematic reviews.

The main studies evaluating structural progression or disease modifying properties in OA ((i) Echodiah study (Dougados *et al.* 2001) with 255 patients in the diacerein arm and 252 under placebo for three years of treatment; and (ii) Pham study (2004) which included 85 patients in the diacerein arm and 85 under placebo during one year) did not show convincing evidence of efficacy of diacerein on pain or physical functioning. In addition, in both cases the study authors reported no difference between groups on analgesic consumption. Only the Dougados study showed efficacy on variables related to a beneficial impact of diacerein on structural progression or disease modifying properties in OA. In the second clinical trial, diacerein was included in one of the control groups in a trial intending to demonstrate the effect of hyaluronic acid intra-articular injections in OA progression which was not demonstrated. The available data were therefore not sufficient to conclude on the structure modifying effects of diacerein in osteoarthritis and no data were available regarding a potential effect of diacerein for delaying surgery.

Finally, several double-blind randomised clinical trials analysed the alleged NSAID sparing effect of diacerein as a secondary endpoint. A reduction in the use of NSAID was only shown in one study and therefore a sparing effect of diacerein on NSAIDs could not be confirmed. However, it was acknowledged that a sparing effect on paracetamol use had been demonstrated in four out of eight clinical trials.

#### *Safety issues*

The PRAC reviewed all available data from clinical studies, published literature, and post-marketing experience on the safety of the diacerein containing products, in particular in relation to the risk of hepatotoxicity, gastro-intestinal disorders and cutaneous disorders.

Diacerein, as other anthraquinone derivatives, has a hepatotoxic effect for which the mechanism of action is unknown. Although it was noted that the data from clinical studies showed no significant differences in hepatic disorders between diacerein and the placebo group, when present, hepatic disorders were in most of cases in the diacerein group. Furthermore, evidence of hepatic reactions was reported, including symptomatic acute liver injury. About 10% of adverse drug reactions (ADR) reported were hepatic disorders and in over 68% of these cases, diacerein was the only drug suspected. Moreover, two cases raised serious concerns: one fatal hepatitis case in which no other reasons of hepatitis except for diacerein could be found; and one case of acute hepatitis with suggestive chronology and no other explanation.

With regards to the risk of gastrointestinal disorders, diarrhoea was a common and expected reaction of diacerein. A laxative effect was observed in up to 50% of the diacerein-treated patients in clinical studies. Some studies revealed that 25% patients with diarrhoea during diacerein treatment experienced chronic diarrhoeas, defined by diarrhoea persisting more than 4 weeks. The high dropout rate due to diarrhoea in clinical trials showed that the acceptability of the treatment was worse in the diacerein group than in the placebo group.

In spontaneous reports, one quarter of serious gastrointestinal cases were related with diarrhoea. The PRAC also noted that spontaneous notifications reported serious cases of diarrhoea with dehydration and electrolyte disorders. Some cases of hospitalisation to further investigate the event of diarrhoea

were also reported. This constituted a concern for the PRAC and it has to be noted that these investigations exposed the patients to invasive examination (i.e. colonoscopy with biopsy). In addition, the management of diarrhoea could also expose patients to symptomatic treatments.

Finally, with regards to the risk of cutaneous disorders, safety concerns were raised with diacerein following a publication of a fatal case of a toxic epidermal necrolysis, with diacerein being the most suspected drug for the events. The present review showed that rash, pruritus and eczema were the most common cutaneous reactions reported in clinical trials but available post-marketing data revealed cases of erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Because of the limited information available on these cases, the PRAC could not conclude on this risk but a cutaneous toxicity of diacerein could not be excluded.

To conclude, the review found that the most frequently reported reactions with diacerein were, as expected, gastrointestinal disorders, especially diarrhoeas, which were frequently severe and leading to complications such as dehydration and disturbances of fluid and electrolyte balance. Furthermore, cases of hepatic enzymes elevations have been reported and as well as serious cases, including a fatal hepatic reaction in a patient treated with diacerein.

#### *Benefit-risk balance*

Having considered the overall submitted data provided by the MAHs in writing and at the oral explanation, the PRAC concluded that the benefit-risk balance of diacerein containing products is not favourable in the currently approved indications.

#### **Re-examination procedure**

Following the adoption of the PRAC recommendation during the November 2013 PRAC meeting, two MAHs expressed their disagreement with the initial recommendation for suspension. The MAHs considered that there is adequate data supporting the efficacy of diacerein in the symptomatic treatment of osteoarthritis of the hip and the knee and proposed further risk minimisation measures to reduce the risk of diarrhoea and potential risk of hepatic reactions associated with diacerein.

The PRAC confirmed it had considered the totality of the data submitted by the MAHs in the context of the initial referral procedure. Notwithstanding this, and given the new proposals from the MAHs on possible measures to minimise the risks, the PRAC carried out a new assessment of the available data in the context of the re-examination.

The PRAC acknowledged that although neither the available randomised clinical trials nor the meta-analyses were without flaws, clinical trials show a modest and statistically significant effect for diacerein in the end-points pain relief and function disability. In addition, meta-analyses confirmed a small but consistent beneficial effect of diacerein on OA symptoms. Diacerein has a delayed initial onset of action and should not be recommended in patients with rapidly progressive hip osteoarthritis, as they may have a weaker response to diacerein. It was reiterated that structure-modifying effects of cartilage by diacerein in OA and long-term efficacy had not been demonstrated by the presented studies; however, a carry-over effect was confirmed by three studies. Furthermore, as previously assessed, a paracetamol sparing effect (in eight trials) and a sparing effect on NSAIDs (in one trial) could be detected, but further research would be needed as proof of evidence.

With regards to the safety profile of diacerein, it was noted that the most frequently reported events with diacerein when used as per label (100mg/day) in the clinical trials, were loose stools and diarrhoea, including severe diarrhoea. It was also noted that in the majority of cases diacerein-induced diarrhoea started soon after treatment initiation, and seemed to be reversible after cessation of

treatment. Hepatic reactions were reported, including symptomatic acute liver injury and one fatal case of fulminant hepatitis. In order to minimise these risks several measures were proposed. These included reducing the posology recommendation at the start of the treatment, and new measures such as a contraindication in patients with liver disease, a strong recommendation for patients to stop treatment as soon as diarrhoea occurs and a restriction of use in patients aged 65 years and above. In addition, given the gastrointestinal risk and potential risk of hepatic reactions, the PRAC considered limiting prescription by specialists experienced in the treatment of osteoarthritis.

With regards to posology, as some patients may experience loose stools or diarrhoea after the intake of two capsules per day during the first few weeks of treatment, it is advisable to start treatment with half the recommended daily dose, i.e. one capsule of diacerein 50 mg per day. Most of transient diarrhoea are reported in the first 2 to 4 weeks and the laxative properties of diacerein seem to be dose-dependent. It was noted that favourable results for the primary criterion, analogue visual scale (VAS) assessment of pain on movement, were shown in patients treated with 50mg/day. In addition, in a comparative study of the efficacy and tolerability of two therapeutic regimens of diacerein (usual treatment (50 mg twice a day) for 3 months versus progressive treatment (50 mg once a day for one month; then 50 mg twice a day for two months) the proportion of patients developing diarrhoea decreased by approx. 10% in the group treated by 50mg once a day followed by 50mg twice a day compared to the group with no titration.

The PRAC considered that it is of importance that patients stop their treatment with diacerein as soon as diarrhoea occurs, in order to prevent diarrhoea complications such as dehydration and hypokalaemia. In addition, warnings were considered necessary for patients receiving concomitantly diuretics, cardiac glycosides or laxatives. It was also concluded that diacerein should no longer be recommended in patients aged 65 years and above as this patient population is more vulnerable to diarrhoea complications. It is acknowledged that OA of the hip and knee is seen more frequently in an elderly population. Therefore, diacerein is still a relevant option for some patients for symptomatic treatment of OA of the hip and knee, but caution is advised and patients must stop treatment should diarrhoea develop.

With regards to the potential risk of hepatic reactions, several hepatic events have been reported, including serious hepatic reactions and one fatal case of hepatitis was reported. The PRAC was of the view that diacerein should be contraindicated in patients with current and/or history of liver disease and that patient should be screened for major causes of active hepatic disease before start of treatment. The product information should reflect the recommendation to monitor signs of hepatic injury and caution should be exercised when diacerein is used concomitantly with other medicinal products associated with hepatic injury. Patients should be advised to limit their alcohol intake while on treatment with diacerein. In addition treatment with diacerein should be stopped if elevation of hepatic enzymes or suspected signs or symptoms of liver damage are detected. To ensure adequate screening of the patients at start of treatment, the PRAC also recommended that diacerein is only initiated by specialists experienced in the treatment of osteoarthritis.

Furthermore, the PRAC considered that periodic updated safety reports (PSURs) should be submitted on a yearly basis. Additional risk minimisation measures within a Risk management Plan were not considered necessary.

### **Overall benefit-risk balance**

Based on the totality of the data available on the safety and the efficacy of diacerein, and considering all the risk minimisation measures proposed during assessment and the re-examination procedure, the PRAC concluded that the benefit-risk balance of diacerein-containing medicinal products remained

favourable in the symptomatic treatment osteoarthritis, subject to changes to the product information and conditions.

### **Grounds for PRAC recommendation**

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for diacerein containing medicinal products;
- The PRAC reviewed all the available data on the efficacy and safety of diacerein-containing medicines in particular data in relation to the risk of hepatotoxicity, gastrointestinal disorders and cutaneous reactions provided by the MAHs in writing and in the oral explanations;
- The PRAC considered the grounds for re-examination provided by the MAHs in writing and in the oral explanations;
- The PRAC considered that the available data supporting the use of diacerein have shown a modest but statistically significant effect in the treatment of osteoarthritis of the knee and hip, with a delayed effect. However, treatment with diacerein is not recommended in patients with rapidly progressive hip osteoarthritis, as they may have a weaker response to diacerein.
- The PRAC considered that available data from pre-clinical studies, clinical trials, post-marketing spontaneous case reports, and published literature have shown that the use of diacerein-containing products is associated with safety concerns such as frequent cases of severe diarrhoea and cases of potentially serious hepatotoxicity; a risk of cutaneous reactions could not be excluded.
- The PRAC considered that several new measures should be implemented to minimise these risks. These included a recommendation to start treatment at half the normal daily dose, a contraindication in patients with a history and/or current liver disease and a clear recommendation for patients to stop treatment as soon as diarrhoea occurs. Also, diacerein is no longer recommended for patients aged 65 years and above. In addition, given the gastrointestinal risk and potential risk of hepatic reactions, the PRAC considered necessary to restrict prescription to specialists experienced in the treatment of osteoarthritis. Finally, information on the cutaneous risk in the Summary of Product Characteristics (SmPC) was considered necessary.
- The PRAC concluded that the risk of severe diarrhoea associated with the use of diacerein containing medicinal products and the occurrence of potentially severe hepatic reactions could be mitigated by the above mentioned risk minimisation measures to be reflected in the SmPC and adequately monitored with yearly PSUR submissions.

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products containing diacerein identified in Annex I remains favourable, subject to the changes to the product information and conditions as provided for in Annex IV.

### **CMDh position**

Having reviewed the final PRAC recommendation dated 6 March 2014 and the revised final PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation. However, the CMDh considered that some changes were necessary in the SmPC and

Package Leaflet (PL) to better reflect the PRAC recommendations and to correct minor discrepancies. The PRAC recommended not to use diacerein-containing medicinal product for patients older than 65 years, but did not consider it as a contraindication. The CMDh therefore considered that any existing information on the recommended dose in this patient population should not be deleted from section 4.2 of the SmPC and section 3 of the PL.

The CMDh also agreed with the PRAC that the PSURs should be submitted on a yearly basis. The agreed new data lock point (DLP) of 31 December 2014 for all diacerein-containing medicinal products will be reflected in the list of Union reference dates (EURD list).

The CMDh, having considered the revised final PRAC recommendation dated 10 July 2014 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached a position on the variation of the marketing authorisations of diacerein containing medicinal products for which the amendments to the product information are set out in annex III and subject to the condition set out in Annex IV.