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Letters to the editor
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Comments on Alegría and Irarrázaval (2017): Is diacerein an alternative for the treatment of osteoarthritis?

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Dear editor:

During my last literature search on Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOA), I came across the Friendly Summary of Body of Evidence using Epistemonikos (FRISBEE) by Alegría and Irarrázaval [1]. Although I found the format of this review on diacerein convenient to read and therefore efficient, I felt that I should provide complementary information and correct one of the assumptions regarding the registration status of diacerein in Europe as I consider them essential for decision-making.

In 2012, following the evaluation of data resulting from pharmacovigilance activities, the French Medicine Agency (ANSM) requested a recommendation on the benefit-risk balance of diacerein-containing products by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA). I have been involved in the safety-related referral procedure as an expert witness representing the company TRB Chemedica. Therefore, please let me take the freedom to clarify the sequence of events.

After the Pharmacovigilance Risk Assessment Committee had initially recommended to suspend the marketing authorisation of diacerein in 2013 [2], additional risk management measures were presented by the marketing authorisation holders in order to reduce the risk of severe diarrhoea and hepatotoxicity associated with the use of the drug. Subsequently, after having performed a re-examination in 2014, the Pharmacovigilance Risk Assessment Committee concluded that the benefit-risk balance of diacerein remained positive in the approved indications [3]. The European Medicines Agency endorsed the Pharmacovigilance Risk Assessment Committee recommendations and therefore, the marketing authorisation of diacerein had never been withdrawn nor suspended in Europe. Thereafter, the referral procedure was underlined by an independent experts' review [4] and a position paper by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [5]. The latter considered diacerein as an interesting option for treating osteoarthritis and positioned it as a first-line pharmacological background therapy, particularly for osteoarthritis patients with comorbidities contraindicating the use of non-steroidal anti-inflammatory drugs or paracetamol.

Another aspect that deserves emphasis is that diacerein is a SYSADOA with an onset of action at two to four weeks, which becomes significant after four to six weeks [6],[7]. As a result, specifying the time point at which pain and functionality improvements are evaluated would make the message of this review more accurate.

Furthermore, I take the opportunity of this letter to draw your attention to an inconsistency between the text and the FRISBEE table; certainty of the evidence is considered moderate for pain and low for functionality in the summary of findings (page 2 of the PDF version), while it is the

opposite in the subsequent table (page 3 of the PDF version).
Finally, I would like to point out that the two clinical trials qualified as ongoing by the authors cannot be regarded as susceptible to modify the current evidence. The first one was conducted in patients with hand osteoarthritis and assessed the efficacy of diacerein versus placebo on pain at one month as primary endpoint, that is a time point too early to expect efficacy of the drug [8]. The second one is an ongoing clinical trial (clinicaltrials.gov NCT02688400) evaluating diacerein versus celecoxib. It will therefore not influence the conclusions of this summary, as it takes into account randomised placebo-controlled clinical trials exclusively.

Notes

Declaration of competing interest
Dr. Leeb represented TRB Chemedica as an expert witness during the referral procedure of the Committee for Pharmacovigilance Risk Assessment in 2013-2014.

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