

## Diacerein: Benefits, Risks and Place in the Management of Osteoarthritis. An Opinion-Based Report from the ESCEO

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**Abstract** Diacerein is a symptomatic slow-acting drug in osteoarthritis (SYSADOA) with anti-inflammatory, anti-catabolic and pro-anabolic properties on cartilage and synovial membrane. It has also recently been shown to have protective effects against subchondral bone remodelling. Following the end of the revision procedure by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) constituted a panel of 11 experts to better define the real place of diacerein in the armamentarium for treating OA. Based on a literature review of clinical trials and meta-analyses, the ESCEO confirms that the efficacy of diacerein is similar to that of non-steroidal anti-inflammatory drugs (NSAIDs) after the first month of treatment, and superior to that of

paracetamol. Additionally, diacerein has shown a prolonged effect on symptoms of several months once treatment was stopped. The use of diacerein is associated with common gastrointestinal disorders such as soft stools and diarrhoea, common mild skin reactions, and, uncommonly, hepatobiliary disorders. However, NSAIDs and paracetamol are known to cause potentially severe hepatic, gastrointestinal, renal, cutaneous and cardiovascular reactions. Therefore, the ESCEO concludes that the benefit–risk balance of diacerein remains positive in the symptomatic treatment of hip and knee osteoarthritis. Furthermore, similarly to other SYSADOAs, the ESCEO positions diacerein as a first-line pharmacological background treatment of osteoarthritis, particularly for patients in whom NSAIDs or paracetamol are contraindicated.

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On behalf of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

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## Key Points

Randomised clinical trials show that diacerein has a similar efficacy compared with NSAIDs on osteoarthritis symptoms.

Diacerein has an acceptable safety profile, particularly in comparison with that of NSAIDs and paracetamol.

The ESCEO positions diacerein as a first-line pharmacological background treatment of osteoarthritis.

## 1 Introduction

Osteoarthritis (OA) is the most frequent form of arthritis, and one of the leading causes of disability among older adults worldwide [1]. For individuals, the burden of OA also includes persistent background pain (aching) and intermittent but generally more intense pain. Together with disability, pain contributes to a significant reduction in quality of life.

The management of OA includes pharmacological therapies, which are mostly symptomatic [2]. Paracetamol is the first-line oral analgesic, whilst oral non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors, are the mainstay of therapy [3, 4]. These drugs are considered as rapid-acting drugs in OA and are recommended by rheumatology societies [2, 5, 6] and government agencies [7].

Symptomatic slow-acting drugs for OA (SYSADOAs) such as glucosamine, chondroitin sulphate and diacerein are used for non-acute treatment. Although there is relative general agreement on many OA management recommendations across organisations, there is still no consensus on the place of SYSADOAs. In general, they are considered supplementary to analgesics and NSAIDs, whereas the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) places SYSADOAs as pharmacological background treatment; that is, first chronic therapy that may improve or control symptoms [8].

Diacerein is an anthraquinone derivative, of which the active metabolite is rhein. Its positioning in the algorithm established by the ESCEO [8] had not been formalised because, at the time of publication, diacerein was under review by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA). Following the assessment of the PRAC, the ESCEO felt the need to evaluate the role of diacerein in

clinical practice and constituted a panel of experts to define its place in the management of OA. This article expresses the reasoned conclusions drawn by the ESCEO working group on diacerein.

## 2 ESCEO Working Group Process

The ESCEO invited 11 experts in musculoskeletal diseases (rheumatologists, clinical epidemiologists and scientists) to be part of the working group. Four members had already been involved in clinical or preclinical research on diacerein, two of them being current diacerein prescribers; all were proficient in analysing and interpreting clinical trial evidence related to OA.

Five of the participants were entrusted with the task of preparing a review on the mode of action, efficacy and safety of diacerein in the treatment of OA. A literature search was conducted in May 2015 using the MEDLINE/PubMed database. The search strategy included a combination of the following terms: ‘diacerein’, ‘diacetylrhein’, ‘diacerhein’, ‘rhein’ and ‘osteoarthritis’. Filter settings were ‘English’, ‘French’, ‘German’, ‘Spanish’ or ‘Italian’ languages. This literature search yielded 179 hits, of which 108 (57 original research papers, 51 reviews, meta-analyses or opinion-based articles) were retrieved according to their relevance to the topics mentioned above: 42 were related to the mode of action of diacerein, 60 dealt with its clinical efficacy, and 45 contained information on the safety of diacerein. Additional references were selected from the reference lists of the retrieved articles to broaden the literature search.

The outcome of this review was finally discussed by the 11 experts at a one-day meeting in June 2015.

## 3 The Mechanism of Action of Diacerein in Osteoarthritis

### 3.1 In Vitro Studies

The principal mechanism of action of diacerein is to inhibit the interleukin-1 $\beta$  (IL-1 $\beta$ ) system and related downstream signalling [9]. Diacerein has been shown to impact the activation of IL-1 $\beta$  via a reduced production of IL-1 converting enzyme [10], as well as to affect the sensitivity to IL-1 by decreasing IL-1 receptor levels on the cell surface of chondrocytes [11] and by indirectly increasing IL-1 receptor antagonist production [12, 13]. Production of IL-1 $\beta$  may also be affected, as diacerein has been shown to inhibit the IL-1 $\beta$ -induced activation of transcription factor NF- $\kappa$ B, which stimulates pro-inflammatory cytokine expression [14–16]. Downregulation of IL-1 levels has

**Table 1** Summary of the effects of diacerein/rhein on articular tissues

Cartilage/synovial membrane	
Anti-catabolic	↓ IL-1 $\beta$ -induced MMP-1, MMP-3, MMP-13, ADAMTS-4, ADAMTS-5 [15, 22] ↓ IL-1 $\beta$ -induced iNOS, NO [13, 16, 19, 23] ↑ IL-1 $\beta$ -induced PGE2, COX-2 [21]
Pro-anabolic	↑ collagen, proteoglycans, hyaluronan [15, 19, 20]
Subchondral bone	
Osteoblasts	↑ PGE2, COX-2 [21] ↓ vitamin D3-induced osteocalcin + ↓ uPA [21] ↓ DKK-1, DKK-2 [24]
Osteoclasts	↓ MMP-13, cathepsin K [25] ↓ osteoclast survival, pre-osteoclast differentiation [25]

Adapted with permission from Martel-Pelletier and Pelletier [9]

*ADAMTS* disintegrin and metalloproteinase domain with thrombospondin motifs, *COX-2* cyclooxygenase-2, *DKK* Dickkopf, *IL-1 $\beta$*  interleukin-1 $\beta$ , antagonist, *iNOS* inducible nitric oxide synthase, *MMP* metalloproteinase, *NO* nitric oxide, *PGE2* prostaglandin E2, *uPA* urokinase-type plasminogen activator

been confirmed in the synovial fluid of patients with knee OA [17].

Besides its anti-inflammatory properties, diacerein has been shown to have anti-catabolic [15, 16] and pro-anabolic [15, 18–20] effects on cartilage and synovial membrane, as well as protective effects against subchondral bone remodelling (Table 1) [21].

### 3.2 Animal Models of Osteoarthritis

Beneficial effects of diacerein on cartilage and subchondral bone have been observed in various animal models of OA. Diacerein consistently reduced cartilage loss compared with untreated controls [26–30], improved cartilage lesions in the experimental hip chondrolysis model of immature Beagle dogs [31], and induced an increase in bone mineral density as well as a decrease in the thickness of the subchondral bone plate [28]. Finally, prophylactic treatment with diacerein has been shown to delay arthritis secondary to meniscectomy in a rat model of OA [32].

## 4 Clinical Data on the Efficacy of Diacerein

### 4.1 Effects on Pain and Physical Function

Efficacy of diacerein was evaluated in 16 published clinical trials [33–48]. Patients included in these studies were representative of patients in a real-life setting, so that the outcomes can be extrapolated to the general population.

Four published meta-analyses assessed the symptomatic effects of 100 mg/day diacerein [49–52]. Each of them included a different set of clinical studies (Table 2).

In a meta-analysis of 19 published and unpublished studies including a total of 2637 patients, Rintelen and co-authors [49] showed a statistically significant superiority of diacerein over placebo at the end of treatment with respect to pain reduction and physical function improvement. At the end of the treatment-free follow-up period, diacerein was also found to be significantly better than placebo on pain (no pooled data on function), thus demonstrating a carry-over effect after stopping treatment. When compared with standard treatments (mostly NSAIDs), no statistically significant difference regarding pain and physical function was observed at the end of the treatment period. However, at the end of the treatment-free follow-up period, pooled Glass' standardised mean differences on pain and joint function showed that diacerein was significantly superior over the active comparator (Fig. 1).

Using the strict Cochrane criteria for meta-analyses, Fidelix and co-authors reviewed seven published randomised controlled trials in a total of 2069 patients with OA [50]. Three more clinical trials [44, 45, 47] were included in the updated Cochrane Review [51] compared with the 2006 version. The main differences in outcomes between the two meta-analyses are shown in Table 3. Thus, in the Cochrane 2014 version, the mean-weighted differences (MWD) tended to increase in favour of diacerein compared with placebo. The authors concluded that diacerein had a small but significant effect on overall pain after 3–36 months of treatment. In addition, results of a subgroup analysis demonstrating a carry-over effect of diacerein compared with placebo or NSAIDs on pain and physical function were presented.

Finally, another meta-analysis on randomised, placebo-controlled trials with diacerein was published by Bartels et al. [52]. The authors included six studies with a total of 1533 patients. The effect size (ES) was estimated using

**Table 2** Clinical studies included in the meta-analyses evaluating diacerein

Study	Blinding	Duration	Control	Rintelen et al. (2006) [49]	Fidelix et al. [50] (Cochrane 2006)	Bartels et al. (2010) [52]	Fidelix et al. [51] (Cochrane 2014)
Fagnani et al. (1998) [36]	Open	6 months	Standard	+			
Chantre et al. (2000) [38]	DB	4 months	DC	+	+		+
Mattara (1985) [53]	DB	3 months	NSAID	+			
Pietrogrande et al. (1985) [54]	DB	1 month	NSAID	+			
Fioravanti and Marcolongo (1985) [55]	DB	2 months	NSAID	+			
Mordini et al. (1986) [56]	DB	2 months	NSAID	+			
Mantia (1987) [57]	DB	3 months	NSAID	+			
Portioli (1987) [58]	DB	3 months	NSAID	+			
Marcolongo et al. (1988) [33]	DB	2 months	NSAID	+			
Tang et al. (2004) [59]/ Zheng et al. (2006) [43]	DB	3 months	NSAID	+	+		+
Louthrenoo et al. (2007) [45]	DB	4 months	NSAID	+			+
Pham et al. (2004) [41]	DB	12 months	NSAID/ i.a. HA	+	+	+	+
Nguyen et al. (1994) [34]	DB	2 months	Placebo/ NSAID	+	+	+	+
Ascherl (1995) [60]	DB	6 months	Placebo	+			
Schulitz (1994) [61]	DB	3 months	Placebo	+			
Lequesne et al. (1998) [37]	DB	6 months	Placebo	+	+	+	+
Pelletier et al. (2000) [39]	DB	4 months	Placebo	+	+	+	+
Dougados et al. (2001) [40]	DB	36 months	Placebo	+	+	+	+
Pavelka et al. (2007) [44]	DB	3 months	Placebo	+		+	+
Brahmachari et al. (2009) [47]	SB	2 months	Placebo				+

DB double-blind, DC Devil's claw or *Harpagophytum procumbens*, HA hyaluronic acid, i.a. intra-articular, NSAID non-steroidal anti-inflammatory drug, SB single-blind

Hedges' standardised mean difference. For pain reduction, results showed that the combined ES was  $-0.24$  (95 % CI  $-0.39$  to  $-0.08$ ,  $p = 0.003$ ,  $I^2 = 56\%$ ), favouring diacerein. There was also a statistically significant improvement in physical function ( $p = 0.01$ ,  $I^2 = 11\%$ ).

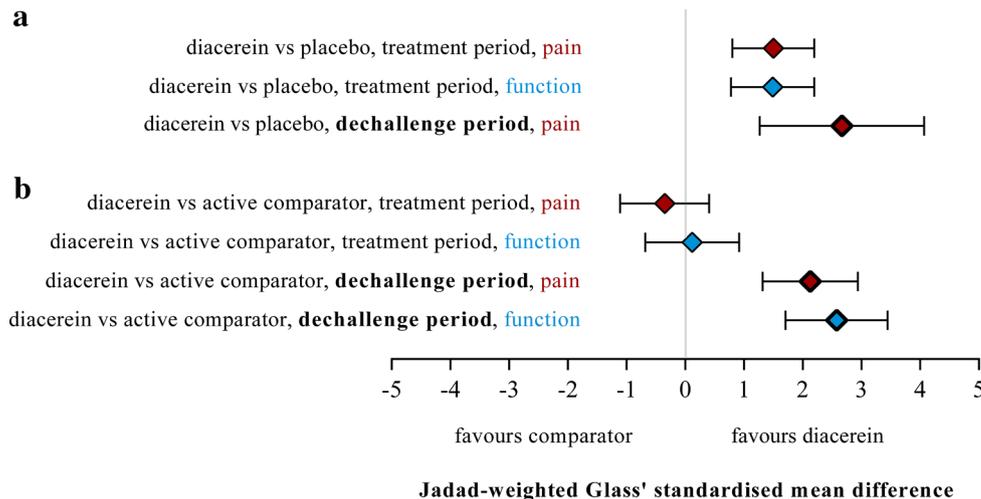
#### 4.2 Structure-Modifying Effects

Two clinical studies assessed the impact of diacerein on radiological signs of OA: one was conducted in patients with hip OA [40], the other in patients with knee OA [41].

The ECHODIAH (Evaluation of the Structure-Modifying Effects of Diacerein in Hip Osteoarthritis) study [40] was a 3-year, multicentre, randomised, double-blind, placebo-controlled trial evaluating the potential structure-modifying effects of diacerein in 507 patients with painful and structurally advanced primary hip OA. Sixty-one patients did not have any pelvic X-ray after the start of treatment and were therefore excluded from the analysis.

The between-group comparison in the number of patients with a joint space narrowing (JSN) of at least 0.5 mm showed a statistically significant difference in

**Fig. 1** Comparison of diacerein vs placebo (a) and diacerein vs active comparator (mostly NSAIDs) (b) regarding pain and physical function at the end of the active treatment period, as well as after the treatment-free follow-up period (dechallenge) (Rintelen et al. [49] meta-analysis). Error bars indicate 95 % confidence intervals. Glass' standardised mean differences greater than 0.8 are commonly regarded as clinically relevant



**Table 3** Main differences in results between the Cochrane Reviews 2006 [50] and 2014 [51]

	Fidelix et al. [50] (Cochrane 2006)	Fidelix et al. [51] (Cochrane 2014)
<b>Diacerein vs placebo</b>		
Pain on VAS (0–100 mm)		
<i>N</i> (no. of studies) – <i>I</i> <sup>2</sup>	1228 (5) – 60 %	1283 (6) – 84 %
WMD (95 % CI)	–5.16 (–9.75 to –0.57)	–8.65 (–15.62 to –1.68)
WOMAC pain subscale (0–500 mm)		
<i>N</i> (no. of studies) – <i>I</i> <sup>2</sup>	234 (1) – NA	399 (2) – 0 %
WMD (95 % CI)	–24.90 (–48.41 to –1.39)	–29.33 (–48.45 to –10.20)
WOMAC function subscale (0–1700 mm)		
<i>N</i> (no. of studies) – <i>I</i> <sup>2</sup>	234 (1) – NA	454 (3) – 0 %
WMD (95 % CI)	–107.50 (–187.51 to –27.49)	–110.92 (–173.88 to –47.97)
<b>Diacerein vs NSAIDs</b>		
Pain on walking on VAS (0–100 mm)		
<i>N</i> (no. of studies) – <i>I</i> <sup>2</sup>	184 (1) – NA	213 (1) – NA
WMD (95 % CI)	–4.61 (–10.69 to 1.47) <sup>a</sup>	1.30 (–3.81 to 6.41)
WOMAC pain subscale (0–500 mm)		
<i>N</i> (no. of studies) – <i>I</i> <sup>2</sup>		161 (1) – NA
WMD (95 % CI)		14.00 (–10.15 to 38.15)
WOMAC function subscale (0–1700 mm)		
<i>N</i> (no. of studies) – <i>I</i> <sup>2</sup>	184 (1) – NA	345 (2) – 0 %
WMD (95 % CI)	–12.28 (–73.01 to 48.45)	29.50 (–23.17 to 82.17) <sup>b</sup>

*N* no. of patients, *NA* not applicable, *I*<sup>2</sup> heterogeneity index *I*<sup>2</sup>, *WMD* weighted-mean difference, 95 % *CI* 95 % confidence interval, *VAS* visual analogue scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Mistakes have been observed in the reporting: <sup>a</sup> values at 4 months of Tang et al. [59] have been included in the analysis instead of values at 3 months (end of treatment); <sup>b</sup> baseline values of Tang et al. [59] have been included in the analysis instead of values at 3 months from Zheng et al. [43]

favour of diacerein in both the intent-to-treat (ITT) and the Completer analyses (primary populations of analysis). The between-group comparison in JSN rate also showed a statistically significant difference in the Completer analysis, while no difference was observed in the ITT population using the last-observation-carried-forward imputation

method. Results in the per protocol (PP) population (secondary analysis) were similar to those in the Completer data set (Table 4).

The above results in the ECHODIAH study demonstrated the superiority of diacerein treatment versus placebo in only three of four co-primary endpoints for JSN

**Table 4** Joint space narrowing measured on pelvic X-ray at 3 years: intent-to-treat, Completer and per protocol data sets (ECHODIAH study by Dougados et al. [40])

Parameter	Diacerein	Placebo	<i>p</i> value
ITT data set, <i>N</i>	221	225	
≥0.5 mm JSN, <i>N</i> (95 % CI)	51 % (44–57)	60 % (54–67)	0.036*
JSN rate (mm/year), mean (SD)	0.39 (0.75)	0.39 (0.81)	ns**
Completer data set, <i>N</i>	131	138	
≥0.5 mm JSN, <i>N</i> (95 % CI)	47 % (39–56)	62 % (54–70)	0.007*
JSN rate (mm/year), mean (SD)	0.18 (0.25)	0.23 (0.23)	0.042**
PP data set, <i>N</i>	101	114	
≥0.5 mm JSN, <i>N</i> (95 % CI)	49 % (38–59)	68 % (58–76)	0.003*
JSN rate (mm/year), mean (SD)	0.18 (0.22)	0.25 (0.23)	0.011**

ITT intent-to-treat, PP per protocol, JSN joint space narrowing, *N* number of patients, 95 % CI 95 % confidence interval, SD standard deviation, ns non-significant

\* Log rank test, \*\* Mann–Whitney test

and failed to demonstrate the structure-modifying effects of diacerein in patients with hip OA.

The Pham study (2004) [41] was conducted in 301 patients with knee OA. The aim of this 1-year, randomised, double-blind, placebo-controlled, three-arm trial was to evaluate the long-term efficacy of three cycles of 3-weekly intra-articular injections of hyaluronic acid (HA) in the treatment of symptomatic knee OA compared with oral diacerein and placebo. A saline solution was used in the diacerein and placebo groups to maintain the blind.

No statistically significant differences between groups were observed for JSN. The percentage of patients with a progression >0.5 mm was 17.7, 18.9 and 20.3 % ( $p = 0.90$ ) in the HA, diacerein and placebo groups, respectively.

## 5 Clinical Data on the Safety of Diacerein

### 5.1 Gastrointestinal

Regarding the risk of gastrointestinal disorders, the most frequently reported events with diacerein were loose stools and diarrhoea. The laxative effect of diacerein is well known and results from its anthraquinone chemical structure.

Bartels et al. [52] calculated that the risk ratio (RR) for developing diarrhoea under diacerein versus placebo treatment was 3.51 (95 % CI 2.55–4.83). Fidelix et al. [51] obtained an RR of 3.52 (95 % CI 2.42–5.11) for diacerein versus placebo, with an absolute risk increase of 24 % (95 % CI 12–35). Well in line with these meta-analyses, Rintelen and co-authors [49] summarised that 39 % of patients treated with diacerein versus 12 % of patients receiving placebo experienced at least one episode of loose stool or diarrhoea.

Diarrhoea was mentioned to be generally mild to moderate in all publications that make reference to the

severity [35, 40, 44], and occurred in the first 2 weeks of treatment. No particular pattern of associated disorders could be detected. In all cases, the diacerein-induced diarrhoea was reversible after cessation of treatment. Furthermore, diarrhoeal symptoms decreased in most cases after continuous treatment [62].

The post-marketing surveillance of diacerein showed that 25 serious cases of diarrhoea were reported. Three of them concerned elderly patients, who experienced dehydration and electrolyte disorders; one case was fatal and occurred in a 79-year-old female with a medical history of arterial hypertension and cardiac arrhythmia [63].

### 5.2 Cutaneous

The skin was not a target organ for toxicity in short- and long-term animal toxicology studies. Nevertheless, the incidence of cutaneous events in the 15 published clinical trials evaluating diacerein ranged between 1.8 % [35, 36] and 9.4 % [41]. The present review identified rash, pruritus and eczema as the most common cutaneous reactions reported in clinical trials. They are appropriately reflected in the product information with a frequency of >1/100 and <1/10).

Furthermore, the available post-marketing data revealed a few severe cases of cutaneous events: four erythema multiform, two Stevens-Johnson syndrome (SJS) and three toxic epidermal necrolysis (TEN) [63].

### 5.3 Hepatic

Among the 15 published clinical trials evaluating diacerein, only Zheng et al. [43] reported the occurrence of a hepatic adverse event: one treatment discontinuation due to increase in hepatic enzymes. The PRAC performed a more complete analysis of available data and retrieved seven clinical trials showing abnormalities of liver tests.

These were mostly characterised by mild/moderate liver enzyme increase (ALT, AST <5 ULN) without increases in bilirubin [63].

A total of 89 cases within the post-marketing surveillance were considered as hepatic reactions. The most frequent reactions were liver function test abnormalities (41 cases) [63]. One case of hepatic failure had a fatal outcome and a close temporal association with diacerein [64].

The extensive preclinical animal toxicology data with diacerein indicated that the liver was not a target organ for toxicity. The mechanism of action of this hepatic toxicity is not fully understood, but an idiosyncratic mechanism is suggested.

#### 5.4 Cardiovascular

Diacerein does not appear to show cardiovascular toxicity. Indeed, a toxicology study designed in accordance with ICH S7A guidelines demonstrated that diacerein at 5 and 30 mg/kg/day for 7 consecutive days, and at 60 and 200 mg/kg/day for 4 and 3 consecutive days, respectively, did not affect the cardiovascular system in the conscious dog [65]. The doses used in this study were between 3.6 times and about 143 times the recommended dose in humans (1.4 mg/kg/day based on a 70 kg person).

More significantly, no signal from post-marketing surveillance for acute coronary syndromes or myocardial infarctions was reported in more than 20 years of experience with diacerein.

## 6 Discussion

The overall analysis of randomised controlled clinical studies and meta-analyses confirmed the efficacy of diacerein in the symptomatic treatment of knee and hip OA. An ES on pain of 0.24 (95 % CI 0.08–0.39) has been reported [52], a value considered to be low but clinically relevant in OA [66]. Furthermore, as the ES of diacerein and other anti-OA agents is based on the difference between the placebo and the active drug effects, it is relevant to note that unequivocal evidence for a large placebo response has been demonstrated in randomised clinical trials of OA (ES = 0.51, 95 % CI 0.46–0.55) [67]. The ES of diacerein should therefore be assessed bearing in mind this large placebo response.

Although NSAIDs have shown a more rapid onset of action than diacerein, efficacy of these drugs on pain and joint function was comparable after the first month of treatment. On the other hand, unlike NSAIDs, diacerein has shown a prolonged effect of several months once treatment was stopped. Evidence published by the Osteoarthritis Research Society International (OARSI) indicated that

diacerein had a greater efficacy on pain reduction in OA than paracetamol (ES = 0.14, 95 % CI 0.05–0.22), and a similar efficacy compared with NSAIDs (ES = 0.29, 95 % CI 0.22–0.35) [6].

The use of diacerein is associated with common gastrointestinal disorders (mostly soft stools and diarrhoea), common mild skin reactions, and uncommon hepatobiliary disorders. Frequent cases of severe diarrhoea and rare cases of potentially serious hepatotoxicity were reported; a risk of cutaneous drug reactions could not be excluded [63].

In order to minimise this risk, it is recommended to start diacerein treatment with half the recommended dose (50 mg/day) for the first 2–4 weeks, the laxative properties of diacerein being dose-dependent [39]. In the same context, starting a treatment with diacerein is not recommended in patients older than 65 years who are considered to be more vulnerable to diarrhoeal complications [68]. In parallel, laxatives should be avoided, and concomitant treatment with medicines that can lead to hypokalaemia should be especially monitored. Finally, it is common sense to stop treatment as soon as diarrhoea occurs. To prevent the risk of hepatotoxicity, diacerein is contraindicated in patients with current or a history of liver disease and, therefore, patients should be screened for major causes of active hepatic disease before starting the treatment. Caution should be exercised when diacerein is used concomitantly with products associated with hepatic injury. Treatment should be stopped if elevation of hepatic enzymes or suspected signs or symptoms of liver damage are detected.

Safety of diacerein should be put in the context of paracetamol and NSAID use, drugs that have been shown to cause potentially severe hepatic [69–71], gastrointestinal [72, 73], renal [74–77], cutaneous [78] and cardiovascular reactions [79–82]. For example, an incidence of clinically apparent liver injuries of 10.0 per 100,000 patient-years of treatment with NSAIDs has been reported [83], and paracetamol is responsible for the higher rate of hospitalisations for hepatic failures [69]. In comparison, the risk of hepatic disorders with diacerein (including elevated hepatic enzymes) was 1.68 per 100,000 patient-years of treatment. Regarding cutaneous reactions, NSAIDs have been reported to be the second most common cause of drug-induced hypersensitivity reaction [84], and among the drugs that are the most frequently associated with SJS and TEN [85]. NSAIDs are also known for increasing the risk of cardiovascular events, including congestive heart failure and infarction/stroke [73, 86, 87].

Several rheumatology societies, such as the European League Against Rheumatism (EULAR) [2] and the OARSI [5, 6], have included diacerein in their therapeutic guidelines as a treatment option in OA. However, a review evaluating the benefit–risk ratio of diacerein conducted by

the PRAC was initiated in November 2012 following the request of the French Medicines Agency. One year later, the PRAC/EMA initially recommended the suspension of the marketing authorisations for diacerein, but following re-examination, additional proposals to manage the risks of diacerein were considered. As a result, in July 2014, the PRAC/EMA confirmed the safety profile of diacerein, which has not changed in 20 years, and concluded that its benefit–risk balance remained positive in the symptomatic treatment of hip and knee OA [63].

Based on the opinion of 11 experts in rheumatology, the ESCEO working group underlines the PRAC/EMA conclusions that the benefits of diacerein outweigh its risks and confirms that diacerein is an interesting option in the physician's armamentarium for treating OA. These conclusions are also in line with those of a review recently published by two independent Australian experts [88]. Therefore, similarly to other SYSADOAs, the ESCEO positions diacerein as a first-line background pharmacological treatment of OA. However, it should be avoided in patients with a known propensity for diarrhoea, but would be particularly beneficial in patients with contraindications to NSAIDs or paracetamol.

Diacerein is a compound with a long history but whose effects are still not fully understood. Besides the evidence of its efficacy in knee and hip OA, there are very few data on its effect in other OA locations such as the hand, as well as on different types of patient profiles [89], or OA subtypes. Further research also needs to be performed to define the real potential of diacerein on disease progression with well designed, high quality, structure-modifying clinical trials. Then, depending on the outcomes on cartilage and knowing the proven carry-over therapeutic effect of diacerein, one might question whether continuous or intermittent treatment would be the most reasonable.

#### Compliance with Ethical Standards

**Authors' contribution** Pr. Reginster organised the meeting. Pr. Bruyère, Pr. Cooper, Dr. Leeb, Pr. Martel-Pelletier and Pr. Pelletier performed the literature review. All authors have taken part in the discussion and meeting and have critically analysed and approved the final manuscript.

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