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The efficacy, safety and carry-over effect of diacerein in the treatment of painful knee osteoarthritis: a randomised, double-blind, NSAID-controlled study[1]

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Summary

Objective: To evaluate the efficacy, safety and carry-over effect of diacerein, in comparison to piroxicam, in the treatment of Thai patients with symptomatic knee osteoarthritis (OA).

Design: This was a double-blind, randomised, piroxicam-controlled, parallel-group study. A 7-day non-steroidal anti-inflammatory drug wash-out period was followed by a 16-week treatment period with either diacerein 100 mg/day or piroxicam 20 mg/day, and an 8-week treatment-free observation period. The primary efficacy criterion was pain on Western Ontario and McMaster University Osteoarthritis (WOMAC) A. The secondary criteria included WOMAC B, C and total WOMAC, paracetamol intake, Short Form-36 questionnaire and global judgements on efficacy and tolerability by patients and investigators.

Results: Of 171 randomised patients, 150 completed the study and 161 were analysed in the intent-to-treat population (diacerein: 82, piroxicam: 79). Pain (WOMAC A) decreased to a similar extent in both groups at Week 16 (diacerein: $-69.7\% \pm 31.5\%$; piroxicam: $-74.1 \pm 26.2\%$; $P =$ n.s.). On treatment discontinuation, pain increased in the piroxicam group at Weeks 20 ($-47\% \pm 47.8\%$) and 24 ($-26.8\% \pm 60.6\%$) while improvements persisted in the diacerein group at Weeks 20 ($-66.9\% \pm 35.9\%$) and 24 ($-69.5\% \pm 33.7\%$), with a significant difference in favour of diacerein at Weeks 20 and 24, demonstrating the carry-over effects of the drug. The incidence of adverse events was similar in both groups but more patients from the piroxicam group dropped out of the study due to these events.

Conclusions: Diacerein was as effective as piroxicam in reducing pain and improving function but, unlike piroxicam, displayed a carry-over effect and a better safety profile.
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Key words: Diacerein, Osteoarthritis, RCT, Piroxicam, SYSADOA, NSAID.

Introduction

Osteoarthritis (OA) is characterised by a progressive degradation and loss of articular cartilage accompanied by subchondral bone remodelling, osteophyte formation and synovial membrane inflammation. The clinical manifestations are a gradual development of joint pain, swelling, instability, stiffness and loss of motion. The incidence of knee OA in some Western European countries has been estimated to be 18–25% in men and 24–40% in women between 60–79 years of age and there are about 100 million persons with knee OA in the European Union[1]. An epidemiological study of an urban Thai population suggested that the prevalence of symptomatic knee OA in Thailand is 34.5% among persons over 60 years of age[2].

The main objectives in the management of OA are to reduce symptoms, minimise functional disability, limit the progression of structural changes and ultimately delay or avoid arthroplasty. Current pharmacological treatment is mostly palliative, with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), including the cyclooxygenase (COX) inhibitors, being the mainstay of therapy.

Research over the last two decades has shown that the cytokine interleukin-1-beta (IL-1β) plays a key role not only in cartilage degradation[3] but also in subchondral

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bone remodelling, chondrocyte apoptosis and joint inflammation[4]. Diacerein, an anthraquinone derivative, is an IL-1β inhibitor[5,6] and is classified as a symptomatic slow acting drug in OA (SYSADOA)[7]. Such drugs have a slow onset of efficacy and a long carry-over effect once treatment is interrupted. As diacerein recently became available in Thailand, we carried out a clinical study to assess the effects of the drug in Thai patients with painful knee OA.

Method

STUDY DESIGN

This was a randomised, multicentre, double-blind, double-dummy, piroxicam-controlled, parallel-group study. All patients provided signed informed consent prior to the study start.

After a 1-week NSAID washout period, patients were randomised to receive either diacerein or piroxicam daily for 16 weeks and this was followed by an 8-week study treatment-free observation period to assess the carry-over effects of both drugs. Patients returned for monthly assessment visits after the baseline visit. Between visits (i.e., at weeks 2, 6, 10, 14), the study nurse or the investigator made telephone calls to the patients to check on patient compliance and comfort. Telephone calls at weeks 18 and 22 were made to ensure compliance to the follow-up period.

The use of NSAIDs was not permitted for the whole duration of the study. Only paracetamol 500 mg tablets (up to 6 times daily) were allowed as rescue analgesia during the whole study period in case of severe pain and patients were asked to record the number of paracetamol tablets used per day in a patient diary. No study medication was provided to the patients during the follow-up period and patients were not told which study drug they received until the study was completed so as not to bias the results during the treatment-free follow-up period.

RANDOMISATION

Each patient was randomly assigned to a treatment group using a randomisation table generated by a validated computer software (RANCODE®, IDV, Gauting, Germany). Treatment allocation depended only on the time sequence in which patients entered the study, thus minimising selection bias.

PATIENT SELECTION

Patients were recruited from rheumatology, orthopaedics or rehabilitation medicine departments of five medical schools in Thailand. Approvals from the appropriate ethics committees were obtained before the study was started. Patients between 40 and 65 years of age, with X-ray confirmed Kellgren–Lawrence[8] grade II or III severity primary tibiofemoral OA, according to the American College of Rheumatology criteria[9], and with knee pain of at least 40 mm on at least two items of the Western Ontario and McMaster University Osteoarthritis (WOMAC) subscale A, using the 100 mm visual analogue scale (VAS), present for at least 15 days in the month prior to study start, were included into the study. Women of childbearing age had to provide evidence of adequate contraception prior to inclusion.

Patients were excluded from the study if any of the following criteria were present: accompanying OA of the hip of sufficient severity to interfere with the functional assessment of the knee; previous or ongoing treatment with oral SYSADOA (e.g., glucosamine sulphate, chondroitin sulphate, diacerein, piascledine), anti-depressants, tranquillisers, antacids or antibiotics; known hypersensitivity to diacerein, to similar compounds, to the excipients or to paracetamol; history of painful knee conditions other than OA; persistent diarrhoea or laxative use; severe gastrointestinal disorders, severe renal insufficiency, hepatic disease, severe obesity, severe parenchymal organ disease, or anaemia (haemoglobin < 10.0 g/dl or haematocrit $< 30\%$). Patients with secondary knee OA, those who received intra-articular treatment of the signal joint with any product (corticosteroids in the previous 2 months, or glycosaminoglycans/hyaluronic acid in the previous 6 months) or had undergone joint lavage and arthroscopic procedures in the previous 6 months, were also excluded.

TREATMENT

Study treatment was either one capsule of diacerein 50 mg and one capsule of placebo for piroxicam, or one capsule of piroxicam 10 mg and one capsule of placebo for diacerein, taken twice daily with the main meals.

EFFICACY PARAMETERS

The primary efficacy criterion was joint pain measured using WOMAC A (VAS). Secondary efficacy variables included joint stiffness (WOMAC B) and physical function (WOMAC C), total WOMAC, Short Form 36 (SF-36) health survey questionnaire, daily paracetamol consumption, global efficacy judgement by the patient and the investigator using a four-point scale (“How well do you feel the treatment has worked thus far?” not effective; slightly effective; moderately effective; very effective), presence of effusion or swelling of soft tissue, and tenderness of the signal joint (VAS) assessed by palpation along the joint line.

SAFETY PARAMETERS

Vital signs were recorded at baseline and at every visit. Blood and urine samples were collected at screening, at Week 8 and at the end of treatment (Week 16) for laboratory safety analyses. Adverse events (AEs) were recorded at each visit and assessed by the investigator. Patients were asked to assess the tolerability of the study treatment globally (“How well did you tolerate the treatment?”) at each visit after baseline using a 5-point rating scale (nil; poor; moderate; good; very good). The investigators also provided a judgement on tolerability (“How well do you think the patient tolerated the treatment?”) using the same scale.

STATISTICAL METHODS

This study was designed to show the non-inferiority of diacerein compared to piroxicam. The study sample size was calculated *a priori* using the statistical programme Nnpar (IDV, Gauting, Germany) based on the Wilcoxon–Mann–Whitney test for two, non-matched groups, for the primary endpoint, WOMAC A at Week 20, i.e., 1 month after the end of treatment. For a medium-sized difference between the groups, i.e., a Mann–Whitney coefficient $= 0.64$ or Cohen effect size $= 0.5$, with a level of significance alpha $= 0.05$ (two-sided) and a power of 80%, it was determined that a sample size $N1 = N2 = 69$ was needed. Considering a 20% drop out

rate, the exact sample size for inclusion was determined to be 168 patients divided into two groups.

Double-data entry was performed in a blind manner using the programme REPORT® (version 6.4.12 from IDV, Gauting, Germany). A validated statistical software TESTIMATE6 (IDV, Gauting, Germany) was used for the analyses and graphical representation of the data.

Three populations (two for efficacy and one for safety) were analysed in the study. The safety population was defined as all randomised patients who had at least one administration of the allocated study product. The two efficacy populations were the intent-to-treat (ITT) population, which consisted of patients who were part of the safety population, had at least one evaluation visit after baseline and no severe protocol deviations; and the per-protocol population (PP), which consisted of patients completing the study according to the protocol with no major protocol deviations.

The Wilcoxon–Mann–Whitney test was used to test for homogeneity of the groups and for differences between groups for the primary and secondary efficacy criteria. The experimentwise multiple level alpha was defined as alpha = 0.025 one-sided, as required for confirmatory studies by the ICH Biostatistics Guideline E9[10].

The confirmatory analysis was performed on the ITT population and the one-sided Wilcoxon–Mann–Whitney test was used as a test for superiority. The sensitivity analyses were performed on the PP population using the same procedures as for the ITT population. Non-parametric tests like the Wilcoxon–Mann–Whitney test were used for the secondary efficacy criteria.

The medical relevance of the differences between groups was quantified using as corresponding effect size the Mann–Whitney (MW) superiority measure and its one-sided 97.5% confidence interval (CI). The MW-measure (0.0–1.0) gives the probability that a randomly selected patient of the test group is 'better off' than a randomly selected patient of the comparator group. Well-known benchmark values[11] are 0.5 = equality; 0.56 = small superiority; 0.64 = medium-sized (relevant) superiority and 0.71 = large superiority.

Results

STUDY PATIENTS

A total of 196 patients were screened and 171 randomised into the study (diacerein: 86 patients, piroxicam: 85 patients). All the randomised patients received at least one dose of study medication. A total of 150 patients completed the study while 21 patients (12.3%) failed to complete due to AEs (six from the piroxicam group and three from the diacerein group), lack of efficacy (three from the piroxicam group and four from the diacerein group), lost to follow up (four patients from the diacerein group) and good response to treatment (one piroxicam-treated patient). The disposition of the patients is provided in Fig. 1.

Ten patients with a severe deviation (i.e., no follow-up assessment after the baseline visit) were excluded from the ITT analysis and six additional patients with major deviations (three non-completers, three with intake of prohibited medication) were excluded from the PP evaluation. Therefore, 161 patients were analysed in the ITT population (diacerein: 82 patients; piroxicam: 79 patients) and 155 in the PP population (diacerein: 78 patients; piroxicam: 77 patients) used for sensitivity analyses. The confirmatory results described here are based on the ITT population. The results of the analyses of the ITT and PP populations were very similar.

BASELINE CHARACTERISTICS

Baseline characteristics of the patients are presented in Table I. There were no significant differences between groups for these parameters. Patients were predominantly female (90.7%) with a mean age of 54 years (±6.6; range 40-67 years). Most patients had either grade II or III OA (Kellgren–Lawrence). However, one patient with grade I OA had severe pain and the investigator decided to include the patient into the study. Of the patients with previous NSAID intake (Table I), 10 (seven in the piroxicam group and three in the diacerein group) previously took piroxicam. There were no relevant differences in baseline values for the other efficacy parameters (Table II).

EFFICACY RESULTS

The mean values and the MW statistics for the efficacy parameters are displayed in Table II. The primary efficacy parameter, pain on WOMAC A, decreased to a similar extent in both groups during the 4-month treatment period: from a mean value of 284.1 ± 65.0 mm VAS at baseline to 84.7 ± 85.8 mm at Week 16 in the diacerein group and from 275.2 ± 63.0 mm at baseline to 70.7 ± 70.0 mm at Week 16 in the piroxicam group. Although piroxicam appeared to have a faster onset of efficacy at Week 4 (mean percent change from baseline was −43.4 ± 27.1% in the piroxicam group and −33.2 ± 34.6% in the diacerein group), the values were nearly similar at Weeks 8 (diacerein: −51.8 ± 34.9%; piroxicam: (−56.3 ± 29.7%;), 12 (diacerein: −64.4 ± 30.9%; piroxicam: −67.8 ± 27.4%) and 16 (diacerein: −69.7 ± 31.5%; piroxicam: −74.1 ± 26.2%). There were no statistically significant differences between groups during the treatment period indicating that the diacerein is as effective as piroxicam for pain reduction.

However, after the treatment interruption, pain increased rapidly in the piroxicam group (from a mean value of 70.7 ± 70.0 mm at Week 16 to 145.2 ± 128.8 mm at Week 20 and 201.3 ± 161.5 mm at Week 24) while it remained stable in the diacerein group (from a mean value of 84.7 ± 85.8 mm at Week 16 to 90.1 ± 91.2 mm at Week 20 and 82.9 ± 88.3 mm at Week 24) with a statistically significant difference in favour of diacerein at Week 20 ($P < 0.0065$) and Week 24 ($P < 0.0001$) (Table II). The mean percent change for WOMAC A is graphically presented in Fig. 2.

The analysis of WOMAC A using MW statistics and appropriate CIs demonstrated a non-inferiority of diacerein treatment at Week 4, but this could not be proven statistically (MW: 0.42 lower bound CI: 0.33). Non-inferiority of diacerein treatment was proven from Week 8 (MW: 0.47, lower bound CI: 0.38) to Week 16 (MW: 0.45, lower bound CI: 0.364). However, the superiority of the diacerein treatment was proven at Weeks 20 (MW: 0.61, lower bound CI: 0.53) and 24 (MW: 0.70, lower bound CI: 0.61) (Table II).

Joint stiffness (WOMAC B), physical function (WOMAC C) and total WOMAC showed the same trend as WOMAC A (Table II). Tenderness on palpation decreased in both groups with a significant difference ($P < 0.0001$) in favour of diacerein only at Week 24. Table III presents the WOMAC values after normalization on a 0–100 mm scale where 0 corresponds to the worst condition and 100 to the best condition.

At baseline, 11 (13.4%) patients in the diacerein group and 12 (15.2%) in the piroxicam group presented joint effusion. At the end of treatment (Week 16), only one patient in each group still presented effusion. At Week 20, three

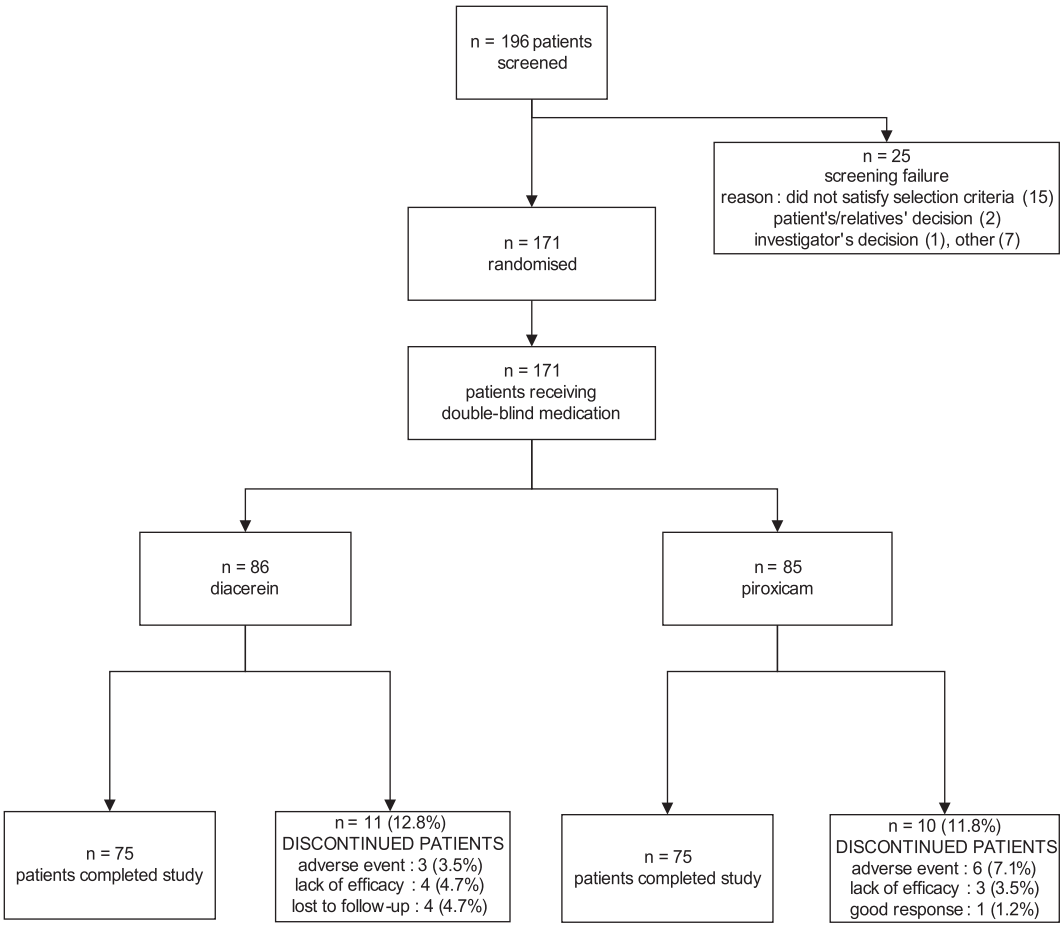

Fig. 1. Disposition of patients.

patients in each group presented effusion and this increased at Week 24 to five (6.1%) and four (5.1%) patients in the diacerein and piroxicam groups, respectively. There were no significant differences between groups during the study and the follow-up period.

Similarly, swelling of the signal joint, which was found in 28 (34.2%) and 29 (36.7%) of the patients in the diacerein and piroxicam groups, respectively, at baseline, decreased in both groups. At Week 16, 10 (12.2%) patients in the diacerein group and seven (8.9%) in the piroxicam group still

Table I
Baseline characteristics

Characteristic		Piroxicam ($n=79$)		Diacerein ($n=82$)		*P*-value*
Gender, *n* (%)	Male	6	(7.6%)	9	(11.0%)	0.59
	Female	73	(92.4%)	73	(89.0%)	
Age (years), *n* (±SD)	Mean	54	(±7.0)	54	(±6.2)	0.93
	Min-max	40–65	–	40–67	–	
BMI (kg/m^2), *n* (±SD)	Mean	26.3	(±3.6)	27.4	(±3.4)	0.13
	Min-max	19.0–34.7	–	20.5–35.8	–	
Kellgren–Lawrence grade, *n* (%)	Grade I	0	(0)	1	(1.2%)	0.34
	Grade II	45	(57.0%)	39	(47.6%)	
	Grade III	34	(43.0%)	42	(51.2%)	
OA bilateral, *n* (%)	No	8	(10.1%)	18	(21.9%)	0.05
	Yes	71	(89.9%)	64	(78.1%)	
OA duration, months (±SD)	Mean	45	(±49.1)	41	(±41.8)	0.95
	Median	35	–	27	–	
	Min-max	1–251	–	1–281	–	
Patients with previous NSAID intake *n* (%)		49	62.0%	43	52.4%	0.27

*Wilcoxon–Mann–Whitney *U* test.

Table II
Efficacy parameters − mean absolute values and MW statistics

	Piroxicam ($n=79$)	Diacerein ($n=82$)	MW	LB, 97.5%-CI	UB, 97.5%-CI	P-value*
WOMAC A (mm ± SD)						
Baseline	275.2 ± 63.0	284.1 ± 65.0	0.45	0.37	0.52	0.25
Week 4	156.2 ± 84.3	190.8 ± 103.6	0.42	0.33	–	0.97
Week 8	119.2 ± 85.9	138.1 ± 99.8	0.47	0.38	–	0.75
Week 12	87.3 ± 74.1	102.0 ± 92.7	0.47	0.38	–	0.74
Week 16	70.7 ± 70.0	84.7 ± 85.8	0.45	0.364	–	0.85
Week 20	145.2 ± 128.8	90.1 ± 91.2	0.61	0.53	–	**0.0065**
Week 24	201.3 ± 161.5	82.9 ± 88.3	0.70	0.61	–	**<0.0001**
WOMAC B (mm ± SD)						
Baseline	114.8 ± 37.5	115.5 ± 40.6	0.502	0.43	0.58	0.97
Week 4	63.2 ± 37.9	79.7 ± 46.5	0.41	0.32	–	0.97
Week 8	52.3 ± 39.8	61.2 ± 44.0	0.45	0.3609	–	0.86
Week 12	38.6 ± 31.2	44.7 ± 41.1	0.47	0.38	–	0.74
Week 16	31.6 ± 32.0	39.5 ± 37.1	0.43	0.34	–	0.94
Week 20	64.5 ± 58.9	36.1 ± 36.4	0.62	0.53	–	**0.0054**
Week 24	56.9 ± 56.2	36.1 ± 37.2	0.58	0.49	–	**0.0360**
WOMAC C (mm ± SD)						
Baseline	865.1 ± 268.3	904.0 ± 272.0	0.46	0.39	0.53	0.39
Week 4	546.6 ± 303.1	653.9 ± 344.1	0.438	0.35	–	0.91
Week 8	433.2 ± 302.5	508.4 ± 341.3	0.47	0.38	–	0.75
Week 12	325.0 ± 267.0	367.5 ± 320.2	0.48	0.40	–	0.63
Week 16	265.4 ± 260.2	301.0 ± 299.1	0.47	0.38	–	0.75
Week 20	448.5 ± 403.5	313.7 ± 327.6	0.59	0.504	–	**0.0217**
Week 24	639.0 ± 516.5	297.8 ± 322.9	0.70	0.61	–	**<0.0001**
WOMAC total (mm ± SD)						
Baseline	1255.2 ± 344.7	1303.6 ± 353.6	0.46	0.38	0.53	0.35
Week 4	766.0 ± 407.6	924.4 ± 479.7	0.42	0.33	–	0.96
Week 8	604.7 ± 416.7	707.6 ± 475.1	0.47	0.38	–	0.76
Week 12	450.9 ± 364.4	514.1 ± 447.2	0.48	0.39	–	0.68
Week 16	367.7 ± 356.1	425.1 ± 414.0	0.46	0.37	–	0.80
Week 20	658.3 ± 566.4	440.2 ± 450.4	0.61	0.52	–	**0.0095**
Week 24	896.6 ± 692.3	416.8 ± 444.0	0.70	0.61	–	**<0.0001**
SF-36 (sumscore)						
Baseline	348.0 ± 104.2	354.9 ± 111.7	0.502	0.43	0.58	0.97
Week 16	558.6 ± 141.4	517.9 ± 146.7	0.41	0.32	–	0.98
Week 24	541.9 ± 159.3	524.1 ± 156.6	0.45	0.36	–	0.86
Paracetamol consumption (tablets/day ± SD)						
Baseline	2.2 ± 1.5	2.0 ± 1.6	0.55	0.48	0.63	0.22
Week 4	0.8 ± 1.0	1.0 ± 1.1	0.43	0.35	–	0.94
Week 8	0.7 ± 1.0	0.9 ± 1.0	0.41	0.33	–	0.98
Week 12	0.6 ± 1.0	0.9 ± 1.0	0.42	0.34	–	0.98
Week 16	0.5 ± 0.9	0.8 ± 1.0	0.42	0.34	–	0.98
Week 20	1.6 ± 1.7	1.0 ± 1.1	0.58	0.5002	–	**0.0273**
Week 24	1.7 ± 1.8	1.0 ± 1.2	0.59	0.5021	–	**0.0247**

MW: Mann−Whitney statistics; LB 97.5%-CI: lower bound of the 97.5% CI. Significant values are in bold.
*Calculated on the median percent change.

presented swelling. This incidence increased in both groups to 14 (17.1%) and 12 (15.2%) in the diacerein and piroxicam groups, respectively, at Week 20, and to 18 (22.0%) and 13 (16.5%) at Week 24.

Both groups demonstrated similar variations in the level of change for each dimension of the SF-36 health survey questionnaire at the end of the treatment period and there were no relevant differences between groups during the study.

The mean intake of paracetamol tablets decreased in both groups until Week 16 (Table II). While intake remained stable during the follow-up period in the diacerein group (1.0 ± 1.1 tablet/day at Week 20 and 1.0 ± 1.2 tablet/day at Week 24), it progressively increased in the piroxicam group (1.6 ± 1.7 tablets/day at Week 20 and 1.7 ± 1.8 tablets/day at Week 24) with a significant difference between groups in favour of diacerein at Weeks 20 ($P=0.0273$) and 24 ($P=0.0247$) (Table II).

The global efficacy judgements by the patients and the investigators are presented in Table IV and confirm the slow onset of efficacy of diacerein with 59.8% in this group compared with 74.7% of the patients in the piroxicam group judging that their treatment was "moderately effective" to "very effective" at Week 4. The judgements were comparable in both treatment groups at the end of the treatment. At Week 20, a significantly ($P<0.0168$) greater proportion of diacerein-treated patients (88.9%) assessed treatment as "moderately effective" to "very effective", compared to 73.1% of those treated with piroxicam while at Week 24 these figures were 86.4% in the diacerein group and 64.1% in the piroxicam group ($P=0.005$).

The relationship of the normalised WOMAC scores and global efficacy judgements (moderate + very effective) by the patients is presented in Table V.

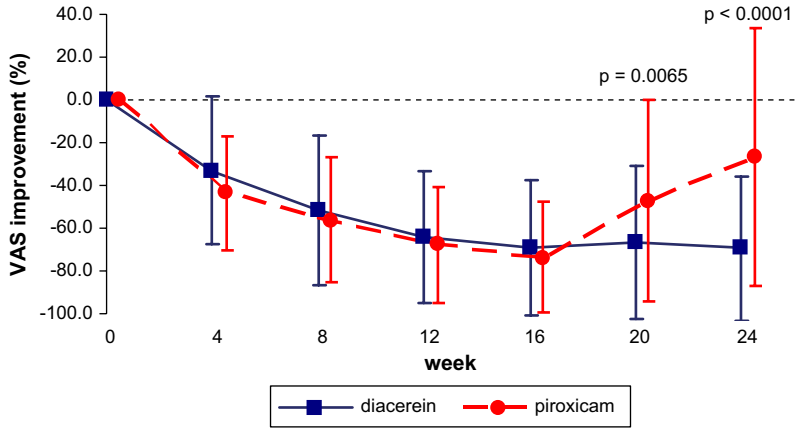

Fig. 2. WOMAC A – mean % change from baseline, SD (ITT population).

SAFETY

During the treatment period, 154 of the 171 randomised patients (90.1%) experienced one or more AEs for a total of 479 AEs. Table VI displays the most commonly observed AEs. Patients were similarly distributed between the diacerein group (79 patients, 91.9%) and the piroxicam group (75 patients, 88.2%). The AEs were of a broad variety and were similarly distributed between the two treatment groups for most event types. Considered by treatment arm, the proportion of patients with AEs in the diacerein group exceeded that in the piroxicam group for urine abnormal (50.0% vs 8.2%), diarrhoea (36.0% vs 10.6%), and bowel motility disorders (soft and/or increased frequency of stools) (12.8% vs 2.4%). The proportion of patients with AE in the piroxicam group exceeded that in the diacerein group for dyspepsia (32.9% vs 22.1%) and oedema (9.4% vs 4.7%). Nine patients (5.3%) withdrew prematurely from the study because of AEs: three patients (3.5%) in the diacerein group and six (7.1%) in the piroxicam group (Table VII). One serious AE (gastrointestinal bleeding) involving patient hospitalisation was reported in the piroxicam group. Vital signs and blood and urine analysis did not reveal any abnormalities.

Both treatments showed good tolerability throughout the study (88.9% of diacerein patients judged the tolerability as "good" to "very good" at Week 16, compared to 92.3% of piroxicam patients). The judgement by the investigators was similar: at Week 16 they evaluated tolerability as "good" or "very good" in 90.1% of the patients treated with diacerein, compared to 92.3% for piroxicam. There was nearly no change in the patients' or investigators' judgements during the follow-up period: the proportion of "good" to "very good" tolerability was about 90% in both groups.

Table III
Results for WOMAC (normalised scale where 0 is the worst condition and 100 is the best condition)

	Piroxicam ($n = 79$)	Diacerein ($n = 82$)
WOMAC A on 100 mm normalised scale (mm ± SD)		
Baseline	45.0 ± 12.6	43.2 ± 13.0
Week 4	68.8 ± 16.9	61.8 ± 20.7
Week 8	76.2 ± 17.2	72.4 ± 20.0
Week 12	82.5 ± 14.8	79.6 ± 18.5
Week 16	85.9 ± 14.0	83.1 ± 17.2
Week 20	71.0 ± 25.8	82.0 ± 18.2
Week 24	59.7 ± 32.3	83.4 ± 17.7
WOMAC B on 100 mm normalised scale (mm ± SD)		
Baseline	42.6 ± 18.8	42.3 ± 20.3
Week 4	68.4 ± 19.0	60.2 ± 23.2
Week 8	73.8 ± 19.9	69.4 ± 22.0
Week 12	80.7 ± 15.6	77.7 ± 20.5
Week 16	84.2 ± 16.0	80.3 ± 18.6
Week 20	67.7 ± 29.4	81.9 ± 18.2
Week 24	71.5 ± 28.2	82.0 ± 18.6
WOMAC C on 100 mm normalised scale (mm ± SD)		
Baseline	49.1 ± 15.8	46.8 ± 16.0
Week 4	67.8 ± 17.8	61.5 ± 20.2
Week 8	74.5 ± 17.8	70.1 ± 20.1
Week 12	80.9 ± 15.7	78.4 ± 18.8
Week 16	84.4 ± 15.3	82.3 ± 17.6
Week 20	73.6 ± 23.7	81.5 ± 19.3
Week 24	62.4 ± 30.4	82.5 ± 19.0
Total WOMAC on 100 mm normalised scale (mm ± SD)		
Baseline	47.7 ± 14.4	45.7 ± 14.7
Week 4	68.1 ± 17.0	61.5 ± 20.0
Week 8	74.8 ± 17.4	70.5 ± 19.8
Week 12	81.2 ± 15.2	78.6 ± 18.6
Week 16	84.7 ± 14.8	82.3 ± 17.3
Week 20	72.6 ± 23.6	81.7 ± 18.8
Week 24	62.1 ± 30.1	82.6 ± 18.5

Discussion

This study was carried out to assess the efficacy and tolerability of diacerein, in comparison with the NSAID, piroxicam, in Thai patients with painful knee OA. Another aim was to assess the carry-over effects of both drugs once treatment was stopped.

Results for the primary efficacy parameter, pain (WOMAC A), showed that the two products caused a reduction in pain every month until the end of the treatment period (Week 16), confirming the results of other randomised, NSAID-controlled studies with diacerein[12–14]. At Week 16, pain showed a mean decrease of 69.7% compared to baseline in the diacerein group, while in the piroxicam group the mean decrease was 74.1%. However, once study treatment was interrupted, symptoms exacerbated rapidly in the piroxicam group while the symptomatic benefits observed at the end of treatment in the diacerein group persisted for a further 2 months, demonstrating the carry-over effects of the drug. This was also seen in a recent randomised, double-dummy, diclofenac-controlled study with diacerein[13].

Table IV
Global efficacy judgements by the patients and the investigator

		Piroxicam ($n=79$)	Diacerein ($n=82$)	MW	LB, 97.5%-CI	*P*-value*
Efficacy judgement by the patient *n* (%)						
Week 4	*n*	79	82	0.42	0.34	0.97
	Not effective	2 (2.5%)	3 (3.7%)			
	Slightly effective	18 (22.8%)	30 (36.6%)			
	Moderately effective	39 (49.4%)	34 (41.5%)			
	Very effective	20 (25.3%)	15 (18.3%)			
Week 16	*n*	78	81	0.51	0.43	0.46
	Not effective	2 (2.6%)	3 (3.7%)			
	Slightly effective	4 (5.1%)	4 (4.9%)			
	Moderately effective	30 (38.5%)	29 (35.8%)			
	Very effective	42 (53.9%)	45 (55.6%)			
Week 20	*n*	78	81	0.59	0.51	**0.0168**
	Not effective	10 (12.8%)	6 (7.4%)			
	Slightly effective	11 (14.1%)	3 (3.7%)			
	Moderately effective	23 (29.5%)	26 (32.1%)			
	Very effective	34 (43.6%)	46 (56.8%)			
Week 24	*n*	78	81	0.62	0.54	**0.005**
	Not effective	16 (20.5%)	7 (8.6%)			
	Slightly effective	12 (15.4%)	4 (4.9%)			
	Moderately effective	17 (21.8%)	24 (29.6%)			
	Very effective	33 (42.3%)	46 (56.8%)			
Efficacy judgement by the investigator *n* (%)						
Week 4	*n*	79	82	0.45	0.37	0.90
	Not effective	1 (1.3%)	3 (3.7%)			
	Slightly effective	20 (25.3%)	25 (30.5%)			
	Moderately effective	40 (50.6%)	40 (48.8%)			
	Very effective	18 (22.8%)	14 (17.1%)			
Week 16	*n*	78	81	0.51	0.43	0.43
	Not effective	2 (2.6%)	2 (2.5%)			
	Slightly effective	3 (3.9%)	6 (7.4%)			
	Moderately effective	30 (38.5%)	26 (32.1%)			
	Very effective	43 (55.1%)	47 (58.0%)			
Week 20	*n*	78	81	0.58	0.49	0.0368
	Not effective	10 (12.8%)	5 (6.2%)			
	Slightly effective	11 (14.1%)	5 (6.2%)			
	Moderately effective	23 (29.5%)	28 (34.6%)			
	Very effective	34 (43.6%)	43 (53.1%)			
Week 24	*n*	78	81	0.62	0.54	**0.0018**
	Not effective	17 (21.8%)	6 (7.4%)			
	Slightly effective	10 (12.8%)	7 (8.6%)			
	Moderately effective	19 (24.4%)	19 (23.5%)			
	Very effective	32 (41.0%)	49 (60.5%)			

*Wilcoxon–Mann–Whitney *U* test for difference (one-sided).

Other randomised, placebo-controlled studies have confirmed that diacerein significantly decreases OA symptoms[12,15]. A 3-year, placebo-controlled structure-modifying study (ECHODIAH)[16] showed that diacerein significantly slowed down cartilage degradation compared to placebo. Hence, it can be assumed that diacerein would have symptomatic effects without deleterious effects on the cartilage.

This difference in activity between the two drugs can be explained by differences in their mechanisms of action. NSAIDs inhibit COX and consequently prostaglandin synthesis, resulting in their analgesic, anti-inflammatory and anti-pyretic effects. However, prostaglandin inhibition also results in the well-known AE profile of NSAIDs, which includes gastrointestinal complications (perforation, ulcers and bleeding) and an increased risk of cardiovascular events such as heart attacks and stroke. In addition, some NSAIDs may have a deleterious effect on cartilage metabolism[17] and may accelerate cartilage degradation on long-term treatment[18]. In the clinical setting, interruption of NSAID treatment leads to a rapid worsening of OA symptoms implying that chronic treatment is required. Although the newer generations of NSAIDs, such as the COX inhibitors, appear to have a slightly better safety profile compared with traditional NSAIDs, they too have been implicated in, among others, severe cardiovascular events which led to worldwide withdrawal of rofecoxib in 2004[19,20]. Hence the side effect profiles of the classical NSAIDs and the newer COX inhibitors indicate that they should be used with care, especially in elderly OA patients with concomitant cardiovascular problems.

In contrast, diacerein is an IL-1β inhibitor in OA with symptom- and structure-modifying properties in OA. *In vitro* studies have shown that at the pre-membrane level, diacerein and its active metabolite rhein down-regulate the activity of IL-1β by significantly decreasing the number of IL-1 receptors on the cell surface[21], by significantly inhibiting

Table V
Normalised WOMAC scores (0–100 scale where 0 is the worst condition and 100 is the best condition) and % patients with moderate + very effective global efficacy judgements

	WOMAC A	WOMAC B	WOMAC C	Total WOMAC	% Patients with moderate + very effective global judgements
Piroxicam					
Baseline	45.0 ± 12.6	42.6 ± 18.8	49.1 ± 15.8	47.7 ± 14.4	
Week 4	68.8 ± 16.9	68.4 ± 19.0	67.8 ± 17.8	68.1 ± 17.0	74.7%
Week 16	85.9 ± 14.0	84.2 ± 16.0	84.4 ± 15.3	84.7 ± 14.8	92.4%
Week 20	71.0 ± 25.8	67.7 ± 29.4	73.6 ± 23.7	72.6 ± 23.6	73.1%
Week 24	59.7 ± 32.3	71.5 ± 28.2	62.4 ± 30.4	62.1 ± 30.1	64.1%
Diacerein					
Baseline	43.2 ± 13.0	42.3 ± 20.3	46.8 ± 16.0	45.7 ± 14.7	
Week 4	61.8 ± 20.7	60.2 ± 23.2	61.5 ± 20.2	61.5 ± 20.0	59.8%
Week 16	83.1 ± 17.2	80.3 ± 18.6	82.3 ± 17.6	82.3 ± 17.3	91.4%
Week 20	82.0 ± 18.2	81.9 ± 18.2	81.5 ± 19.3	81.7 ± 18.8	88.9%
Week 24	83.4 ± 17.7	82.0 ± 18.6	82.5 ± 19.0	82.6 ± 18.5	86.4%

the binding of IL-1 to its receptor[21] and by significantly increasing the release of IL-1 receptor antagonist[6].

At the post-membrane level, diacerein inhibits the release of inflammatory and cartilage degrading factors, most probably by inhibiting the activation of nuclear factor-kappa B[22], while stimulating the production of cartilage growth factors such as transforming growth factor-beta and cartilage components, even in the presence of IL-1β[23,24]. This may explain the cartilage protective effects of diacerein seen in animal models of OA[24–28], in the 3-year structure-modifying ECHODIAH study[16], and also the carry-over effects seen in this and in other clinical studies with the drug[13,29].

Concerning safety, although a similar incidence of AEs was observed in both treatment groups, more severe events were observed in the NSAID group. One patient in the piroxicam group was hospitalised due to gastrointestinal haemorrhage during the treatment period. In contrast, no cases of upper gastrointestinal (GI) tract events, such as gastric or duodenal ulcers, were reported in the diacerein group. This is due to the finding that diacerein does not inhibit COX and hence, prostaglandins[30].

The major AE reported with diacerein was urine discolouration, a known event with this drug class. This is due to the elimination of diacerein metabolites via the kidney, and is of no clinical significance[31]. The high incidence of upper respiratory tract infections in our study was not previously observed in other clinical trials with diacerein and may be attributed to seasonal factors. Although the incidence of diarrhoea, also a known drug class event, was higher in the diacerein group, this did not lead to any patient dropping out of the study and the event may be considered more as patient discomfort.

In conclusion, given that the efficacy of diacerein is similar to that of piroxicam and other NSAIDs such as tenoxicam[12], diclofenac[13], but has a better safety profile with a long carry-over effect, the product could be safely used instead of NSAIDs for the treatment of painful OA. Indeed, a recent metaanalysis of seven randomised clinical trials (RCTs)[32] with diacerein, classified as "platinum" level of evidence, showed that diacerein has a small, consistent benefit in improvement in pain. Another recent metaanalysis, based on 19 RCTs with diacerein involving 2637 patients, confirmed these results and provided further evidence for a statistically significant and clinically relevant efficacy of diacerein on pain and function in OA patients[33]. Diacerein was significantly superior to placebo during the active treatment phase and during the treatment-free follow-up period. When compared to NSAIDs, diacerein was similarly efficacious during the treatment period but unlike NSAIDs, showed a long carry-over effect once treatment was interrupted.

Table VI
Most commonly observed treatment-emergent AEs (in ≥5% of patients in either treatment group)

	Piroxicam ($n = 85$) *n* (%)	Diacerein ($n = 86$) *n* (%)
Urinary system disorders		
Urine abnormal	7 (8.2%)	43 (50.0%)
Respiratory system disorders		
Upper respiratory tract infection	21 (24.7%)	26 (30.2%)
Gastro-intestinal system disorders		
Dyspepsia	28 (32.9%)	19 (22.1%)
Diarrhoea	9 (10.6%)	31 (36.0%)
Abdominal pain	10 (11.8%)	8 (9.3%)
Bowel motility disorders	2 (2.4%)	11 (12.8%)
Constipation	5 (5.9%)	4 (4.7%)
Nausea	2 (2.4%)	5 (5.8%)
Cardiovascular disorders, general		
Hypertension	10 (11.8%)	8 (9.3%)
Musculo-skeletal system disorders		
Myalgia	7 (8.2%)	11 (12.8%)
Arthropathy*	6 (7.1%)	1 (1.2%)
Body as a whole – general disorders		
Oedema	8 (9.4%)	4 (4.7%)
Central and peripheral nervous system disorders		
Dizziness	4 (4.7%)	5 (5.8%)

*The term "arthropathy" is related to treatment efficacy.

Table VII
AEs leading to discontinuation from study

	Piroxicam ($n = 85$)	Diacerein ($n = 86$)	Total ($n = 171$)
Dyspepsia	2 (2.4%)	1 (1.2%)	3 (1.8%)
Oedema*	2 (2.4%)	0	2 (1.2%)
Asthenia*	1 (1.2%)	0	1 (0.6%)
GI haemorrhage	1 (1.2%)	0	1 (0.6%)
Abdominal pain	1 (1.2%)	0	1 (0.6%)
Myalgia	0	1 (1.2%)	1 (0.6%)
Gastritis	0	1 (1.2%)	1 (0.6%)

*Oedema and asthenia were recorded simultaneously for one patient.

However, as diacerein has a slow onset of efficacy, and given that it does not inhibit prostaglandins, the drug can be safely co-prescribed with an NSAID for the first 2–4 weeks of treatment in order to obtain a faster symptomatic relief for the patients[29]. Indeed, an endoscopic study showed that diacerein would protect the gastric mucosa from NSAID toxicity[34]. Finally, diacerein could be especially useful in elderly OA patients with cardiovascular problems that preclude the use of NSAIDs.

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References

1. Altman RD, Abramson S, Bruyere O, Clegg D, Herrero-Beaumont G, Maheu E, *et al*. Commentary: osteoarthritis of the knee and glucosamine. Osteoarthritis Cartilage 2006;14:963–6.
2. Kuptniratsaikul V, Tosayanonda O, Nilganuwong S, Thamalikitkul V. The epidemiology of osteoarthritis of the knee in elderly patients living an urban area of Bangkok. J Med Assoc Thai 2002;85:154–61.
3. Pelletier JP, DiBattista JA, Roughley P, McCollum R, Martel-Pelletier J. Cytokines and inflammation in cartilage degradation. Rheum Dis Clin North Am 1993;19: 545–68.
4. Pelletier JP, Martel-Pelletier J. Therapeutic targets in osteoarthritis: from today to tomorrow with new imaging technology. Ann Rheum Dis 2003;62(Suppl 2):ii79–82.
5. Moldovan F, Pelletier J-P, Jolicoeur FC, Cloutier JM, Martel-Pelletier J. Diacerhein and rhein reduce the ICE-induced IL-1β and IL-18 activation in human osteoarthritic cartilage. Osteoarthritis Cartilage 2000;8:186–96.
6. Yaron M, Shirazi I, Yaron I. Anti-interleukin-1 effects of diacerein and rhein in human osteoarthritic synovial tissue and cartilage cultures. Osteoarthritis Cartilage 1999b;7:272–80.
7. Lequesne M. Symptomatic slow-acting drugs in osteoarthritis: a novel therapeutic concept? Rev Rhum Engl Ed 1994;61:69–73.
8. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16:494–502.
9. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Arthritis Rheum 1986; 29:1039–49.
10. International Conference on Harmonisation of Technical. Requirements for Registration of Pharmaceuticals for Human Use (ICH). Topic E9. Statistical principles for clinical trials. Step 4. Consensus Guidelines. February 5. 1998: CPMP Ref. CPMP/ICH/363–96.
11. Colditz GA, Miller JN, Mosteller F. Measuring gain in the evaluation of medical technology. The probability of a better outcome. Int J Technol Assess Health Care 1988;4:637–42.
12. Nguyen M, Dougados M, Berdah L, Amor B. Diacerhein in the treatment of osteoarthritis of the hip. Arthritis Rheum 1994;37:529–36.
13. Zheng WJ, Tang FL, Li J, Zhang FC, Li ZG, Su Y, *et al*. Efficacy and safety of diacerein in osteoarthritis of the knee: a randomized, multicenter, double-dummy, diclofenac-controlled trial in China. APLAR J Rheumatol 2006;9:64–9.
14. Marcolongo R, Fioravanti A, Adami S, Tozzi E, Mian M, Zampieri A. Efficacy and tolerability of Diacerhein in the treatment of osteoarthrosis. Curr Ther Res 1988; 43:878–87.
15. Pelletier JP, Yaron M, Haraoui B, Cohen P, Nahir MA, Choquette D, *et al*. Efficacy and safety of diacerein in osteoarthritis of the knee: a double-blind, placebo-controlled trial. The Diacerein Study Group. Arthritis Rheum 2000b;43:2339–48.
16. Dougados M, Nguyen M, Berdah L, Mazieres B, Vignon E, Lequesne M. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Arthritis Rheum 2001;44:2539–47.
17. Jones AC, Doherty M. The treatment of osteoarthritis. Br J Clin Pharmacol 1992;33:357–63.
18. Huskisson EC, Berry H, Gishen P, Jubb RW, Whitehead J. Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. LINK Study Group. Longitudinal Investigation of nonsteroidal antiinflammatory drugs in knee osteoarthritis. J Rheumatol 1995;22:1941–6.
19. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004;364: 2021–9.
20. Horton R. Vioxx, the implosion of Merck, and aftershocks at the FDA. Lancet 2004;364:1995–6.
21. Martel-Pelletier J, Mineau F, Jolicoeur FC, Cloutier JM, Pelletier JP. *In vitro* effects of diacerhein and rhein on interleukin 1 and tumor necrosis factor-alpha systems in human osteoarthritic synovium and chondrocytes. J Rheumatol 1998;25:753–62.
22. Ferreira-Mendes AF, Caramona MM, de Carvalho AP, Lopes MC. Diacerhein and rhein prevent interleukin-1beta-induced nuclear factor-kappaB activation by inhibiting the degradation of inhibitor kappaB-alpha. Pharmacol Toxicol 2002;91:22–8.
23. Felisaz N, Boumediene K, Ghayor C, Herrouin JF, Bogdanowicz P, Galerra P, *et al*. Stimulating effect of diacerein on TGF-β1 and β2 expression in articular chondrocytes cultured with and without interleukin-1. Osteoarthritis Cartilage 1999;7:255–64.
24. Douni E, Sfikakis PP, Haralambous S, Fernandes P, Kollias G. Attenuation of inflammatory polyarthritis in TNF transgenic mice by diacerein: comparative analysis with dexamethasone, methotrexate and anti-TNF protocols. Arthritis Res Ther 2004;6: R65–72.
25. Smith GN Jr, Myers SL, Brandt KD, Mickler EA, Albrecht ME. Diacerhein treatment reduces the severity of osteoarthritis in the canine cruciate-deficiency model of osteoarthritis. Arthritis Rheum 1999;42: 545–54.
26. Brandt KD, Smith G, Kang SY, Myers S, O'Connor B, Albrecht M. Effects of diacerhein in an accelerated canine model of osteoarthritis. Osteoarthritis Cartilage 1997;5:438–49.
27. Ghosh P, Xu A, Hwa SY, Burkhardt D, Little C. [Evaluation of the effects of diacerhein in the sheep model of arthritis]. Rev Prat 1998;48(Suppl 17): S24–30.

28. Mazieres B, Berda L. Effect of diacerhein (ART 50) on an experimental post-contusive model of OA. Osteoarthritis Cartilage 1993;1:47.
29. Lequesne M, Berdah L, Gerentes I. [Efficacy and tolerance of diacerhein in the treatment of gonarthrosis and coxarthrosis]. Rev Prat 1998;48(Suppl 17): S31–5.
30. Pelletier JP, Mineau F, Fernandes JC, Duval N, Martel-Pelletier J. Diacerhein and rhein reduce the interleukin 1β stimulated inducible nitric oxide synthesis level and activity while stimulating cyclooxygenase-2 synthesis in human osteoarthritic chondrocytes. J Rheumatol 1998;25:2417–24.
31. Nicolas P, Tod M, Padoin C, Petitjean O. Clinical pharmacokinetics of diacerein. Clin Pharmacokinet 1998; 35:347–59.
32. Fidelix TSA, Soares BGDO, Trevisani VFM. Diacerein for osteoarthritis (Review). Cochrane Database Syst Rev 2006;1:1–59.
33. Rintelen B, Neumann K, Leeb BF. A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. Arch Intern Med 2006;166:1899–906.
34. Petrillo M, Montrone F, Ardizzone S, Caruso I, Bianchi-Porro G. Endoscopic evaluation of Diacethylrhein-induced gastric mucosal lesions. Curr Ther Res 1991;49:10–5.