# Efficacy and tolerance of an oral enzyme combination in painful osteoarthritis of the hip. A double-blind, randomised study comparing oral enzymes with non-steroidal anti-inflammatory drugs

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## Abstract

### Objective

*The objective of this study was to establish the non-inferiority of an oral enzyme therapy (Phlogenzym® -(PE)) as compared to the non-steroidal anti-inflammatory drug (NSAID) diclofenac (DC) in patients with osteoarthritis (OA) of the hip.*

### Methods

*Ninety patients presenting with painful episodes of OA of the hip were treated for 6 weeks in one study centre in a phase III, randomised, double blind, parallel group trial. Altogether, 45 patients were treated in the PE group and 45 patients were treated in the DC group. Primary efficacy criteria were: WOMAC dimensions pain, joint stiffness and function, and Lequesne index as multiple endpoint according to O'Brien. The efficacy criteria were analysed applying the test of non-inferiority with regard to mean changes and frequencies, t-test, U test, ANCOVA and descriptive methods.*

### Results

*Within the 6 weeks observation period, the adjusted changes from baseline to endpoint of the target parameters worked out as follows (adjusted differences, mean ± SEM): WOMAC subscale pain (PE -10.3 ± 1.2, DC -9.5 ± 1.2), WOMAC subscale joint stiffness (PE -3.9 ± 0.5, DC -3.6 ± 0.5), WOMAC subscale physical function (PE -31.7 ± 3.5, DC -29.7 ± 3.5), Lequesne's index (PE -2.89 ± 0.47, DC -2.27 ± 0.47). Non-inferiority of PE as compared to DC with regard to the O'Brien's global sum of the standardised adjusted changes from baseline to endpoint in pain, stiffness, physical function, and Lequesne's index was established with $p = 0.0025$. PE was simultaneously non-inferior as compared to DC with regard to the 4 single endpoints: WOMAC subscale pain ($p = 0.0033$), WOMAC subscale joint stiffness ($p = 0.0061$), WOMAC subscale physical function ($p = 0.0039$), Lequesne's index ($p = 0.0008$) (closed test procedure). The equivalence tests remained insignificant due to comparatively lower effects of DC. For 71.1% of the PE patients and for 61.4% of the DC patients rates of good or very good global investigator assessments of efficacy were calculated (test of non-inferiority: $p = 0.0011$). In the majority of patients, tolerability was judged in both drug groups as very good or good.*

### Conclusion

*This trial showed significant non-inferiority from 6 weeks treatment with PE in patients with OA of the hip with regard to the WOMAC dimensions pain, stiffness and physical function, to Lequesne's index, to the investigator and patients assessments of efficacy, and to the responder rates based on pain, physical function, and patient assessment of efficacy. With regard to drug tolerability some tendencies in favour of PE were detected. However, in this study there was no real difference between PE and DC 100 mg/day, implying an equal benefit-risk relation between the substances. PE may well be recommended for the treatment of patients with osteoarthritis of the hip with signs of inflammation as indicated by a high pain level.*

### Key words

Diclofenac, oral enzymes, osteoarthritis of the hip, pain, randomised trial.

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## Introduction

Osteoarthritis (OA) is a prevalent and costly joint disease with the clinical manifestations of pain, stiffness and limitation of movement due to the cartilage loss and local inflammation. OA of the hip is a chronic degenerative, non-systemic joint disease that occurs prevailingly in patients older than 65 years, with increasing incidence with age. There is a clear preference in postmenopausal female patients (1-3).

Standard therapy for patients presenting with painful episodes are non-steroidal anti-inflammatory drugs (NSAID). NSAID belong to the group of rapid-onset symptom-modifying drugs, and are widely prescribed as a first-line therapy for relief of symptoms, although they do not modify the disease itself. Their prolonged or repeated use often is associated with an increased risk of gastric and duodenal ulcers and upper gastrointestinal perforation and bleeding (4-6). Out of the many NSAID available, diclofenac is one of the most commonly used drugs, as it is regarded as one of the better tolerated NSAID (7). Other therapies combining anti-inflammatory and pain reducing efficacy in patients with painful heap of osteoarthritis of the hip are definitely of interest, the more so if they offer a better risk-benefit ratio. This is the case for an orally applied enzyme-rutoside combination (PE) containing the enzymes bromelain and trypsin and the flavonoid rutoside. The hydrolase trypsin is extracted from porcine pancreas, the endopeptidase bromelain extracted from the juice of the trunk of the ripe pineapple and the flavonoid rutoside trihydrate is extracted from the seed of the Japanese pagoda tree. The drug was shown to be of equal or even superior efficacy when compared with NSAID in patients with osteoarthritis (8-11). Bromelain, trypsin and rutosid are absorbed in the upper intestine. After absorption trypsin and bromelain are bound to anti-proteinases such as $\alpha_2$-macroglobulin and $\alpha_1$-antitrypsin. This binding covers the antigenic determinants and the specific hydrolytic activity is maintained. The combination of both serin- and cystein-proteases is logical, as the different enzymes do have different substrate specificity. The mechanism of action of enzymes is not fully understood, but there is a variety of effects which are thought to contribute to their clinical efficacy. Rutin is metabolised very quickly to its active metabolites 3,4-dihydroxy-phenyl acetic acid and homovanillic acid, concentrations of which have been detected in blood, and which are pharmacologically active (12, 13). Pharmacological investigations of PE in animals have proven no toxic, teratogenic or mutagenic characteristics after a single, multiple or long-term intake (14, 15).

The aim of this clinical study was to establish the non-inferiority of PE as compared to the standard diclofenac in patients with osteoarthritis of the hip with regard to a multiple efficacy endpoint based on changes from baseline to endpoint in the WOMAC dimension pain, in the WOMAC dimension joint stiffness, in the WOMAC dimension physical function and in Lequesne's index.

## Patients and methods

*Study patients*

The study was conducted at one specialised rheumatology centre in Austria from October 1999 to November 2001. Men and non-pregnant women suffering from OA of the hip with pain lasting for at least 3 months were eligible if they were at least 20 years old, had a radiological or CT proven sign of OA (reduced joint cavity, development of osteophytes, subchondral sclerosis), WOMAC (Western Ontario and McMasters Osteoarthritis Index) VRS subscale pain (≥ 20 points of 50 possible points), Lequesne's pain and functional index ≥ 10 and ≤ 14. The hip joint which was the primary source of pain or disability was designated "study joint".

Patients were not eligible if they had a concurrent medical or arthritic disease or abnormal laboratory results that had the potential to confound or interfere with the efficacy evaluation or pose an additional risk to the patient; history of allergy to study drugs, hypersensitivity to paracetamol or any other NSAID; or received an investigational drug within 30 days of screening; intraarticular steroids or hyaluronic acid injection(s) in the affected joint within 2 months, or

systemic steroids within 4 weeks before screening.

*Ethical conduct*

The study was approved by the Ethics Committee of the State of Salzburg and written informed consent was obtained from all the study patients prior to entering the study. The study was performed according to the guidelines of Good Clinical Practice and the Declaration of Helsinki.

*Treatments*

The PE study medication was provided as enteric coated tablets (Phlogenzym®; Mucos Pharma, Geretsried, Germany) containing bromelain 90 mg, trypsin 48 mg and rutosid 100 mg. Each enteric coated DC tablet (Allvoran® TAD Pharma, Cuxhaven, Germany) contained 50 mg DC sodium. PE was administered as two tablets t.i.d., DC as one tablet b.i.d. One treatment group received PE active and DC placebo, and the other group received PE placebo and DC active (double dummy technique). No gastric antisecretive therapy was administered. Treatment compliance was checked after 3 and 6 weeks by pill-counting. Patient were not allowed to receive treatments that might interfere with their OA, such as locally or systemically administered antirheumatics, antiphlogistics or analgesics, intraarticular adrenocortical steroid or hyaluronic acid injections, or injections with other substances in the affected joint, systemic adrenocortical administrations, or physical therapy such as electrotherapy at the affected joint. Only in the case of insufficient efficacy, paracetamol 500 mg tablets were allowed as "rescue medication" up to a maximum dosage of 2000 mg daily. The consumption of rescue medication was documented in the CRF.

*Study design and outcome variables*

This study was designed as non-inferiority, double blind, randomised, active comparator-controlled trial with 6 weeks of treatment (first 3 weeks as in-patients, last 3 weeks as out-patients), in accordance with published recommendations and the typical duration of other OA studies (16, 17). Examinations were performed at baseline, and at scheduled visits at week 3 and 6. Primary efficacy criteria were Lequesne's index (17) and the WOMAC index (18). Patients completed the WOMAC OA index with a patient-administered questionnaire consisting of 24 Visual Rating Scale (VRS) questions (5 regarding pain, 2 regarding stiffness and 17 regarding physical function). The rating scales are divided into 11 equal boxes (for scoring from 0 to 10). The three WOMAC dimensions concern Pain, Joint stiffness and Physical functions with ranges of the subscales from 0-50 for pain, 0-20 for joint stiffness and 0-170 for physical function. The Lequesne index uses the subscales Pain, Walking and Activity of daily living with ranges from 0-8 in each section. The total Lequesne index score ranges from 0-24. The global judgement of efficacy by patient and by investigator was reported on a 4-point categorical scale ranging from 1 (bad) to 4 (very good). Safety measurements included the reporting of adverse events and a global judgement of safety by patient and by investigator, again on a 4-point categorical scale ranging from 1 (bad) to 4 (very good). Laboratory samples (haematology, clinical chemistry, urinalysis) were taken at baseline, during the study, and at the end of the study.

*Statistical methods*

The objective of the statistical analysis was to establish non-inferiority of PE as compared to DC with respect to the O'Brien (19, 20) global sum of the four single endpoints (difference post-pre of WOMAC dimension pain, difference post-pre of WOMAC dimension joint stiffness, difference post-pre of WOMAC dimension physical function and difference post-pre of Lequesne's index). The differences were adjusted separately for baseline values by means of ANCOVA (analysis of variance), standardized (mean 0, standard deviation 1), and added up to O'Brien's global sum. Further target variables of the confirmatory statistics were the items of the primary efficacy variable as single endpoint, the global investigator and patient assessment of efficacy and the responder rates defined according to Dougados (21). In case of quantitative parameters, the equivalence limit E was defined by the formula $E = \sigma/2$ with $\sigma$ = SD of the respective effect variable following DC. In case of responder rates, the equivalence limit E was fixed: E = 20%. The tests of non-inferiority were carried out one-tailed according to the confidence interval inclusion method, $\alpha = 0.025$ was used as significance level.

## Results

*Recruitment*

Ninety patients (45 PE, 45 DC) were enrolled in the study (Table I), randomised and treated (safety population). The full analysis set of patients for intention-to-treat analysis consisted of 88 subjects (FAS), and the number of patients without major protocol violations for per protocol analysis was 72 (valid case set). Comparison of baseline demographic and other baseline characteristics of all patients included into the study did not reveal relevant differences between the two treatment groups.

The WOMAC total index in the baseline status of OA varied between 68 and 194 and was 121.6 ± 22.5 on average ± SD. Lequesne's index varied between 10.0 and 14.0 and was 11.44 ± 1.24 on average ± SD (Fig. 3).

*Efficacy results*

The results for the ANCOVA of changes from baseline to endpoint of the target parameters within the 6 weeks observation period for the intention-to-treat analysis (FAS) are displayed in Figure 1. Non-inferiority of PE as compared to DC with regard to the O'Brien's global sum of the standardised adjusted changes from baseline to endpoint in pain (P), stiffness (S), physical function (F), and Lequesne's index (L) was established with $p = 0.0025$ (Table II). Due to the comparatively weaker treatment effects in the DC group the consecutive 2nd part of the equivalence test remained insignificant. PE was simultaneously non-inferior as compared to DC with regard to the 4 single endpoints in a closed test procedure. At the fourth level of the procedure, the single scales were classified as non-inferior as follows: WOMAC subscale pain ($p = 0.0033$), WOMAC subscale

**Table I.** Demographic and other baseline characteristics.

| Variable | PE Group N = 45 | DC Group N = 45 |
|---|---|---|
| Demography | | |
| Age, mean (years/SD) | 51.2/8.5 | 53.1/8.2 |
| Gender, male/female | 25/20 | 34/11 |
| Body height, mean (cm/SD) male, female | 175/6 160/7 | 173/6 161/6 |
| Body weight, mean (kg/SD) male, female | 85.6/9.3 69.5/11.2 | 81.6/9.0 72.9/10.9 |
| Body mass index (kg/m²/SD) | 27.5/3.3 | 27.4/3.3 |
| Caucasian ethnic origin | 45 | 45 |
| Diagnosis and main disease related criteria | | |
| Most affected side (right/left) | 24/21 | 25/20 |
| Nocturnal pain (no/yes) | 5/40 | 2/43 |
| Pain at rest (no/yes) | 3/42 | -/45 |
| Pain on movement (no/yes) | -/45 | -/45 |
| Duration of recurrent complaints, median (months) | 60.0 | 73.0 |
| Duration of proven OA, median (months) | 54.0 | 60.0 |
| Radiological evidence of OA (≤ 1 year/ >1 year) | 44/1 | 41/3 (one missing) |
| Number of treated episodes in the last 12 mos, median | 3.5 | 3.0 |
| Duration of actual episode, median (months) | 2.0 | 3.0 |
| Pre-medication of actual episode (no/yes) | 19/26 | 20/25 |

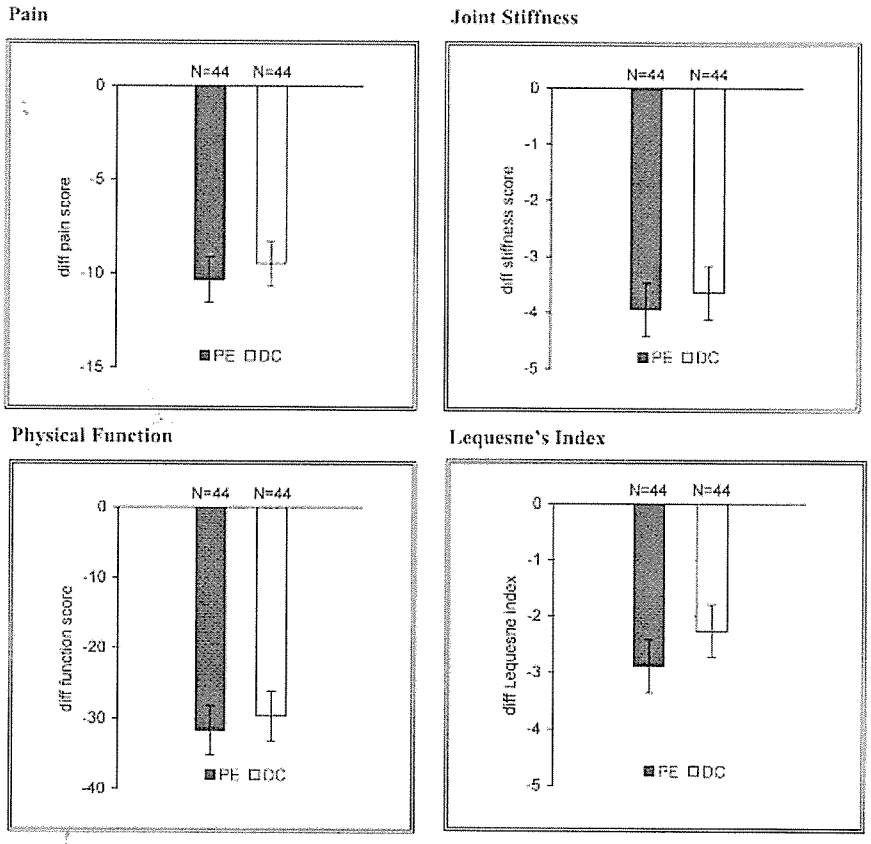


**Fig. 1.** Mean adjusted changes from baseline to endpoint (diff ± SEM) in the WOMAC subscale Pain, WOMAC subscale Joint Stiffness, WOMAC subscale Physical Function, and Lequesne's Index in the intention-to-treat analysis.

joint stiffness (p = 0.0061), WOMAC subscale physical function (p=0.0039), and Lequesne's index (p = 0.0008); (Fig. 2). The non-inferiority test for the per protocol analysis set (PE N = 36, DC N=36; p=0.0006) showed an even clearer tendency in favour of PE with a treatment difference of 1.05±0.79 and a 95% confidence limit of -2.63/0.53.

The rates of good or very good global investigator assessments of efficacy (Table III) were 72.1% in the PE group, and 61.4% in the DC group (test of non-inferiority: p = 0.0011). The rates of good or very good global patient assessments of efficacy were 62.8% in the PE group, and 50.0% in the DC group (test of non-inferiority: p = 0.0009). Responders were 75.0% of the PE patients, and 68.2% of the DC patients (test of non-inferiority: p = 0.0026). The results represented in the full analysis set were excellently confirmed in the valid case set. The rates of good or very good investigator global assessment of efficacy were 77.8% in the PE group and 63.9% in the DC group (test of non-inferiority: p = 0.0007). The rates of good or very good patient global assessment of efficacy were 69.4% in the PE group and 55.6% of the DC group (test of non-inferiority: p=0.0013). Responders were 80.6% of the PE patients and 66.7% of the DC patients (test of non-inferiority: p = 0.0005) (Table III). The PE group showed significant non-inferiority as compared to DC with regard to all primary and secondary endpoints intended for non-inferiority testing. The respective equivalence tests remained insignificant without exception due to partly marked differences in favour of the enzyme preparation. Results for the time point 3 weeks are displayed for Lequesne's index (Fig. 3) showing that oral enzyme therapy was equally effective at this time.

The duration of trial drug administration ranged between 2 and 46 days (PE) and between 13 and 45 days (DC). No relevant differences between trial groups were detected with regard to the extent of study drug exposure. Rescue medication was used in a minor subgroup of the whole study population and no differences between the study groups could be detected.

*Drug safety*

A total of 46 patients (23 in each study group) out of the 90 study patients (51.1%) suffered at least one adverse event. In the PE group 11 (24.4%) of these events were classified as possibly study drug related, and 13 (28.9%) in the DC group. Gastrointestinal disorders were the most frequent events attributed to the study medications. There were 2 serious adverse events, 1 in the DC group and 1 in the PE group, all of them of moderate intensity and not

**Table II.** Test of non-inferiority of PE as compared to DC with respect to the O'Brien global sum (FAS).

| O'Brien global sum of the standardized adjusted changes from baseline to endpoint in the variables WOMAC pain, WOMAC stiffness, WOMAC function, Lequesne index | | |
|---|---|---|
| • PE (N = 44) | (mean ± SD) | -0.25 ± 3.59 |
| • DC (N = 44) | (mean ± SD) | 0.25 ± 3.18 |
| Equivalence limit $E = \sigma_{DC}/2$ | | 1.59 |
| Treatment difference $\Delta_{PE} - \Delta_{DC}$ | (mean ± SEM) | −0.49 ± 0.72 |
| 95% confidence limit ($CI_{lower}$ \| $CI_{upper}$) of $\Delta_{PE} - \Delta_{DC}$ | | (−1.93 \| 0.94) |
| Non-inferiority test | ($CI_{upper} < E$) | p = 0.0025 |
| Non-inferiority established on $\alpha = 0.025$ level? | | YES |

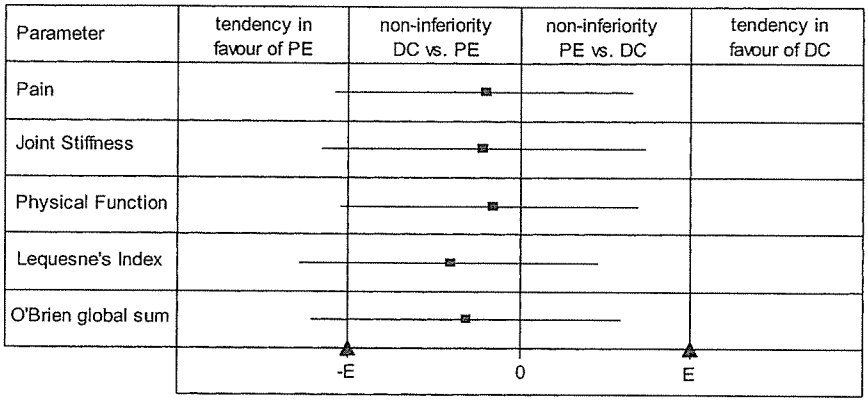


**Fig. 2.** Tests of non-inferiority of PE vs. DC in the intention-to-treat analysis. (E = equivalence limit).

**Table III.** Global assessment of efficacy and responder rates (ITT, VC).

| Global assessment of efficacy and responder rates (ITT) | PE | DC |
|---|---|---|
| Investigator global assessment of efficacy (test of non-inferiority: p = 0.0011) | 31/43 (72.1%) | 27/44 (61.4%) |
| Patient global assessment of efficacy (test of non-inferiority: p = 0.0009) | 27/43 (62.8%) | 22/44 (50.0%) |
| Responder rates (test of non-inferiority: p = 0.0026) | 33/44 (75.0%) | 30/44 (68.2%) |
| Global assessment of efficacy and responder rates (VC) | | |
| Investigator global assessment of efficacy (test of non-inferiority: p = 0.0007) | 28/36 (77.8%) | 23/36 (63.9%) |
| Patient global assessment of efficacy (test of non-inferiority: p = 0.0013) | 25/36 (69.4%) | 20/36 (55.6%) |
| Responder rates (test of non-inferiority: p = 0.0005) | 29/36 (80.6%) | 24/36 (66.7%) |

ITT: Intention to treat; VC: valid case.

directly attributed to the respective study medication. The rate of discontinuations due to adverse events was 13.3% in the DC group (6/45) and 11.1% (5/45) in the PE group.

In the DC group there was a relevant increase of GPT (2.2±8.5 U/L), whereas GPT (1.6±4.4 U/L) and γ-GT (3.3± 9.5 U/L) were decreased in the PE group. This result is consistent with the FDA drug label for DC (warnings / hepatic effects: increase in liver enzymes; elevation of one or more liver tests). With regard to haematology there was a noticeable decrease of erythrocytes (0.08 ±0.20 $10^6$/μU/L), haemoglobin (0.27 ± 0.58 g/L), and haematocrit (0.74 ± 1.66%) in the DC group. This effect is also mentioned by the FDA drug label for DC under precautions / haematologic effects: anaemia. With regard to these laboratory findings there was no indication for problems in the PE group.

## Discussion

Osteoarthritis of the hip is characterized by inflammation caused by degeneration or trauma of the hip limited to this joint, by a loss of hyaline cartilage, pain and increasing loss of function develop after overload and trauma. The aim of treatment is to reduce disease progression, inflammation, pain, and loss of function. NSAID are the drugs of choice in the treatment of inflammatory reactions in different types of arthritis (22, 23), reducing both pain and stiffness and therefore improving patients quality of life. The most commonly applied drug is diclofenac, which was used for standard comparison in this study. The main problem of all NSAID is their risk of adverse effects (6, 24). Although overall NSAID are safe drugs, gastrointestinal intolerance is their major side-effect.

Because of the adverse effects of NSAID, alternative drug therapy should be sought. Enzyme treatment might provide this alternative. The enzyme preparation under test has demonstrated a marked anti-inflammatory effect in many preclinical and clinical studies (25, 26). Systemic enzyme therapy intervenes in four different processes: the release of inflammatory mediators, the modulation of adhesion molecules, the dissolution of detritus and the activation of fibrolysis with consequent improved healing. Additionally, enzymes reduce immune complexes, which play a role in the pathogenesis of inflammatory rheumatic diseases. Thus, healing is accelerated.

The antioxidative compound in the test drug, rutin, eliminates radicals. A retrospective epidemiological cohort study with PE in rheumatic diseases showed that the onset of the effect of NSAID is faster, while the effect of enzyme preparations lasts longer (8). To avoid gas-

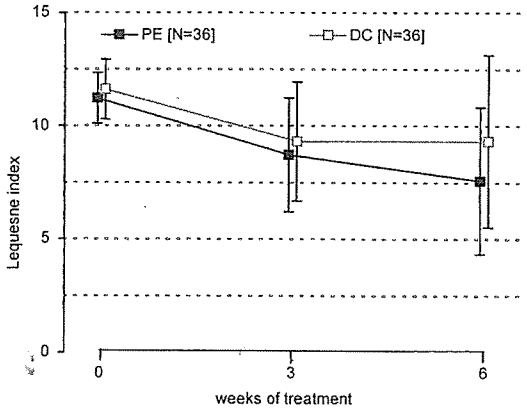


**Fig. 3.** Lequesne's index in the course of treatment (means ± SD)

trointestinal complications as far as possible, the dose of diclofenac in the present study was chosen as 50 mg b.i.d. as it is known that short-term treatment with this dose preserves efficacy but limits adverse effects. When higher doses or longer diclofenac therapy are required, adverse effects rapidly increase. Although the rate of related adverse events does not differ between treatments DC showed some undesired hepatic (increase in liver enzymes) and haematologic (anaemia) side effects. Our study supports the hypothesis that in patients suffering from a disease flare of OA of the hip with acute pain, PE is equally efficacious to diclofenac. Equal efficacy was proven for all primary criteria, and thus was well established across a broad range of parameters assessing pain and function.

This trial showed significant non-inferiority of PE 2 tablets t.i.d. versus DC 1 tablet b.i.d. with regard to the WOMAC dimensions pain, stiffness and physical function, to Lequesne's index, to the investigator and patients assessments of efficacy, and to the responder rates based on pain, physical function, and patient assessment of efficacy. The opposite tests of DC versus PE and, therefore, the tests of equivalence were insignificant without exception. With regard to drug tolerability some tendencies in favour of PE were detected. This observation is in agreement with reports from other studies (8-11), and thus may imply a better benefit-risk relation for PE as compared to DC so that PE may well be recommended for the treatment of patients with osteoarthritis of the hip.

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