Clin Rheumatol (2004) 23: 410–415
DOI 10.1007/s10067-004-0902-y

2337

ORIGINAL ARTICLE

Naseer M. Akhtar · Rizwan Naseer · Abid Z. Farooqi
Wajahat Aziz · Mussadeq Nazir

Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee – a double-blind prospective randomized study

Received: 28 April 2003 / Accepted: 23 January 2004 / Published online: 24 July 2004

Abstract The aim of this study was to compare the efficacy and safety of an oral enzyme–rutosid combination (ERC) containing rutosid and the enzymes bromelain and trypsin, with that of diclofenac in patients with osteoarthritis (OA) of the knee. A total of 103 patients presenting with painful episodes of OA of the knee were treated for 6 weeks in two study centers in a randomized, double-blind, parallel group trial. Altogether, 52 patients were treated in the ERC group and 51 patients were treated in the diclofenac group. Primary efficacy criteria were Lequesne's Algofunctional Index (LFI) and a 'complaint index', including pain at rest, pain on motion and restricted function. The efficacy criteria were analyzed by applying the Wilcoxon–Mann–Whitney test that provides the Mann–Whitney estimator (MW) as a measure of relevance. Non-inferiority was considered to be proven if the lower bound of the 97.5% one-sided confidence interval (CI-LB) was higher than MW = 0.36 (benchmark of not yet relevant inferiority). Both treatments resulted in clear improvements. Within the 6-week observation period, the mean value of the LFI decreased from 13.0 to 9.4 in the ERC group and from 12.5 to 9.4 in the diclofenac group. Non-inferiority of ERC was demonstrated by both primary criteria, LFI (MW = 0.5305; CI-LB = 0.4171) and complaint index (MW = 0.5434; CI-LB = 0.4296). Considerable improvements were also seen in secondary efficacy criteria, with a slight tendency towards superiority of ERC. The global judgment of efficacy by physician resulted in at least good ratings for 51.4% of the ERC patients, and for 37.2% of the diclofenac patients. In the majority of patients tolerability was judged in both drug groups as very good or good. The current study indicates that ERC can be considered as an effective and safe alternative to NSAIDs such as diclofenac in the treatment of painful episodes of OA of the knee. Placebo-controlled studies are now needed to confirm these results.

Keywords Diclofenac · Oral enzymes · Osteoarthritis · Pain · Randomized trial

Abbreviations ERC: Enzyme–rutosid combination · LFI: Lequesne's Algofunctional Index

Introduction

Osteoarthritis (OA) of the knee is a common joint disorder causing pain and disability of varying severity. An inflammation component in OA is established [1, 2]. Standard therapy for patients presenting with painful episodes are non-steroidal anti-inflammatory drugs (NSAIDs). NSAID belong to the group of rapid-onset symptom-modifying drugs, and are widely prescribed as a basic therapy for relief of symptoms, although they do not modify the disease itself. The maximum efficacy of NSAIDs is usually reached within 2 weeks. Their prolonged or repeated use is often associated with an increased risk of gastric and duodenal ulcers and upper gastrointestinal perforation and bleeding [3, 4]. Out of the many NSAIDs available, diclofenac is one of the most commonly used as it is regarded as one of the better tolerated NSAIDs [5].

Other therapies combining anti-inflammatory and pain-reducing efficacy in patients with painful episodes of OA of the knee are definitely of interest, the more so if they offer a better risk:benefit ratio. This is the case for

Dr. Mehnaz Rashid was the Clinical Trials monitor on behalf of Pacific Pharmaceuticals (Lahore, Pakistan) and Dr. W. Schiess played the same role on behalf of Mucos Pharma (Germany)

N. M. Akhtar · R. Naseer
Pakistan King Edward Medical College Lahore,
Mayo Hospital, Lahore, Pakistan

A. Z. Farooqi (✉) · W. Aziz · M. Nazir
Department of Rheumatology,
Pakistan Institute of Medical Sciences, Sector G8/3,
Islamabad, Pakistan
E-mail: afarooqi@isb.paknet.com.pk
Tel.: +92-051-9260112

an orally applied enzyme–rutosid combination (ERC) Phlogenzym, (Mucos Pharma, Geretsried, Germany) containing rutosid and the plant cysteine endoproteinase bromelain (EC 3.4.22.32) and the animal serine endoproteinase trypsin (EC 3.4.21.4). In a large epidemiological cohort study [6] the drug was shown to be superior to NSAIDs in patients with OA.

Bromelain, trypsin and rutosid are absorbed in the upper intestine. The enzymes are bound to antiproteinases. Bromelain lowers bradykinin. Trypsin enhances fibrinolysis, and together both enzymes lower the proinflammatory cytokines (i.e. TNF-α, IL-1, IFN-γ). Rutosid is a flavonoid compound which inhibits hyaluronidase in connective tissues, the blockage of ATPases, phospholipases, cyclo-oxygenases and lipo-oxygenases, thus providing an additional edema-protective effect. Rutin also has anti oxidative properties. Rutosid is immediately metabolized to its active metabolites homovanillic acid (HVA) and 3,4-dihydroxy-phenyl-acetic-acid (DOPAC). Rutosid and its primary metabolites reduce the production of cytokine IL-1$\beta$and TNF-α. The combination of both serin- and cystein-proteases is logical, as the different enzymes do have different substrate specificities. 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, such as antiedematous effects and effects on antiproteinases and α_2-macroglobulin. In the context of osteoarthritis effects on cytokines may be of special interest. Bromelain is the enzyme for which most data are available. Pharmacological investigations in animals have proved no toxic, teratogenic or mutagenic characteristics for the test drug ERC after a single, multiple or long-term intake [7, 8].

The aim of this clinical study was to determine whether the effectiveness described for diclofenac in patients with OA of the knee suffering from a disease flare could also be achieved with ERC.

Materials and methods

A total of 96 male and female outpatients suffering from radiologically confirmed OA of the knee with a disease flare in one knee joint (target joint) were planned to be included at two clinical centers in Pakistan. The main inclusion criterion was a Lequesne's Functional Index (LFI) score ≥10. Subjects pretreated for OA within 2 weeks prior to baseline, with rheumatoid arthritis or diseases causing secondary arthritis, were excluded. Also excluded were patients having had systemic or intra-articular treatment with corticosteroids within the previous 2 months.

The study was approved by the Hospitals' Institutional Review Board and written informed consent was obtained from all participants prior to entering the study. The study was performed according to the guidelines of Good Clinical Practice and the Declaration of Helsinki.

Each active enteric-coated enzyme tablet of ERC (Phlogenzym; Mucos Pharma, Geretsried, Germany) contained bromelain 90 mg, trypsin 48 mg and rutosid 100 mg. Each active enteric-coated diclofenac tablet (Duravolten, Durachemie, Wolfsrathausen, Germany) contained 50 mg of diclofenac sodium. ERC was administered thrice daily, diclofenac twice daily. The dose of diclofenac was chosen to minimize adverse effects and the risk to patients [9]. One treatment group received ERC active and diclofenac placebo, and the other group received ERC placebo and diclofenac active (double dummy technique). Treatment compliance was checked at each visit by pill counting.

Study design and outcome variables

In accordance with published recommendations and the typical duration of other OA studies, the study was designed as a double-blind, randomized, active comparator-controlled trial with 6 weeks of treatment [10, 11]. Examinations were performed at baseline, and at scheduled office visits at weeks 2, 4, and 6.

Primary efficacy criteria were Lequesne's Algofunctional Index (LFI) [12] and a complaint index including pain at rest and on motion, as well as restricted function. Each of the three domains of the complaint index was rated on a visual analog scale (VAS) ranging from 0 (best) to 10 (worst). The complaint index was calculated as the sum of the three judgments (range 0–30). Secondary efficacy criteria were judgment of disability on a 5-point categorical scale ranging from 1 (light) to 5 (unbearable), judgment of therapy result by the patient on a 7-point categorical scale ranging from 1 (much better) to 7 (much worse), pain-free range of joint motion (angle in degrees); and circumference (cm) of the affected knee. Also a global judgment of efficacy by physician and patient was assessed with a 5-point categorical scale ranging from 1 (very good) to 5 (poor).

Safety measurements included the reporting of adverse events and a global judgment of safety by both patient and investigator, again on a 5-point categorical scale ranging from 1 (very good) to 5 (poor). Laboratory samples (hematology, biochemistry) were taken at baseline and at the end of the study.

Statistical methods

A test for non-inferiority was performed by applying the Wilcoxon–Mann–Whitney test, providing the Mann–Whitney estimator as a measure of relevance. The interpretation of the Mann–Whitney statistic (MW) is: 0.50 = no difference; 0.44 // 0.56 = small difference; 0.36 // 0.64 = medium difference; 0.29 // 0.71 = large difference [13].

The analyses were performed as one-sided tests with 97.5% confidence intervals. Non-inferiority was considered to be proven if the lower bound of the confidence

interval was higher than MW = 0.36 (benchmark of not yet relevant inferiority). Data analyses were carried out based on the ITT and the per protocol population (PP). According to the principle of a priori ordered hypotheses, four hypotheses were tested with full level alpha ($\alpha = 0.025$, one-sided):

- First hypothesis: test for non-inferiority of ERC vs. diclofenac (LFI; ITT Population);
- Second hypothesis: test for non-inferiority of ERC vs. diclofenac (complaint index); ITT population
- Third hypothesis: test for non-inferiority of ERC vs. diclofenac (LFI); PP population
- Fourth hypothesis: test for non-inferiority of ERC vs. diclofenac (complaint index); PP population.

Secondary criteria were evaluated in a descriptive manner. Missing values were substituted by the last value carried forward technique. Continuous data were evaluated as percentage change from baseline at week 6, categorical data as found at week 6.

Results

The first patient was included in February 1999, and the last patient finished the study in June 2000. Out of 116 randomized patients (ERC 56/diclofenac 60) 103 patients were treated with the study medication (ERC 51/diclofenac 51). The ITT population included 98 patients (ERC 46/diclofencac 52). A total of 56 patients (ERC 24/diclofenac 32) was evaluated in the PP population. Comparison of baseline demographic and other baseline characteristics did not reveal relevant differences between the two treatment groups (Table 1). A total of 20 patients (ERC 10/diclofenac 10) discontinued the study prematurely (Table 2). About half of the study participants received physical therapy during the study, such as massage, isometric quadriceps exercise or underwater treatment, equally distributed between the two groups.

Efficacy results are presented for the ITT population. Within the 6-week observation period, the mean value of the LFI decreased from 13.0 to 9.4 in the ERC group (mean decrease 26.3%) and from 12.5 to 9.4 in the diclofenac group (mean decrease 23.6%) (Fig. 1). Non-inferiority of ERC was demonstrated (MW = 0.5305; CI-LB = 0.4171). In the same period the mean complaint index decreased from 4.9 to 3.5 in the ERC group (mean decrease 30.2%) and from 4.9 to 3.6 in the diclofenac group (mean decrease 26.6%) (Fig. 2). Again, non-inferiority of ERC could be demonstrated (MW = 0.5434; CI-LB = 0.4296). The results of the ITT analyses are supported by those of the PP analyses (Fig. 3).

Until week 6, the patients of both treatment groups (ITT) experienced considerable improvements concerning the secondary efficacy criteria pain at rest (median decrease: ERC: 41.0%/diclofenac: 22.5%; MW = 0.5601, CI-LB = 0.4328) and pain on motion (median decrease in both groups 28.6%; MW = 0.5079, CI-LB = 0.3941). For the criterion restricted function a median decrease of 10.0% was found in the ERC group, but there was no median decrease in the diclofenac group (MW = 0.5256; CI-LB = 0.4149). According to the investigators' judgment the handicap concerning the affected knee at week 6 was at least bearable in 84.5% of patients in the ERC group, compared to 80.8% in the diclofenac group (MW = 0.5483; CI-LB = 0.4436). At week 6 the therapeutic result was rated "much better" by 24.4% of the ERC patients and by 19.2% of the diclofenac patients (MW = 0.5667; CI-LB = 0.4547). The global judgment of efficacy by physician resulted in at least "good" ratings in 51.4% of the ERC patients and 37.2% of the diclofenac patients (MW = 0.5619; CI-LB = 0.4456). A similar result was found for the global judgment of efficacy by patients (MW = 0.5682; CI-LB = 0.4453). Concerning pain-free range of joint motion of the affected knee median changes from baseline were not

Table 1 Demographic and disease characteristics at baseline (ITT population)

Variable	ERC group (n=46)	Diclofenac group (n=52)
Demography		
Age, mean (years/SD)	57.2/9.66	56.0/10.19
Sex, male/female	14/32	14/38
Weight, mean (kg/SD)	76.2/20.34	75.2/12.25
Height, mean (cm/SD)	163.4/10.01	163.3/8.67
Disease-related criteria		
Affected side: right side/ left side/both sides (no. of patients)	24/20/2	20/31/1
Cause: degenerative/ traumatic/other	42/4/0	48/4/0
Duration of complaints, mean (months /SD)	52.5/48.57	48.9/49.78
Efficacy criteria		
LFI (points /SD)	13.0/2.78	12.5/2.53
Pain at rest (cm VAS/SD)	2.7/1.80	2.6/2.00
Pain on motion (cm VAS/SD)	6.7/1.57	6.7/1.25
Function restricted (cm VAS/SD)	5.3/1.45	5.3/1.62
Angle painfree motion (degrees/SD)	118.1/13.72	115.7/17.53
Circumference target sjoint (cm/SD)	40.7/4.80	40.7/3.97
Circumference (cm/SD) contralateral joint	40.3/4.95	40.2/4.07

Table 2 Study termination; ITT population

Reason	ERC	Diclofenac
According to protocol	36 (78.3%)	42 (80.8%)
Due to insufficient efficacy	2 (4.4%)	2 (3.9%)
Due to adverse event (AE)	4 (8.7%)	1 (1.9%)
Due to insufficient efficacy and AE	1 (2.2%)	2 (3.9%)
Withdrawal of consent	1 (2.2%)	1 (1.9%)
Lost to follow-up	1 (2.2%)	4 (7.7%)
Others	1 (2.2%)	0 (0.0%)
Valid no.	46	52

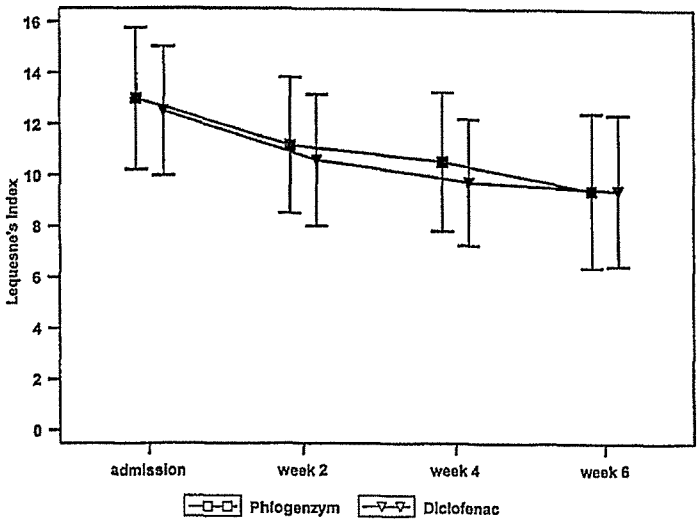


Fig. 1 Index of severity for knee osteoporosis (LFI), means and standard deviations, missing values replaced by LVCF

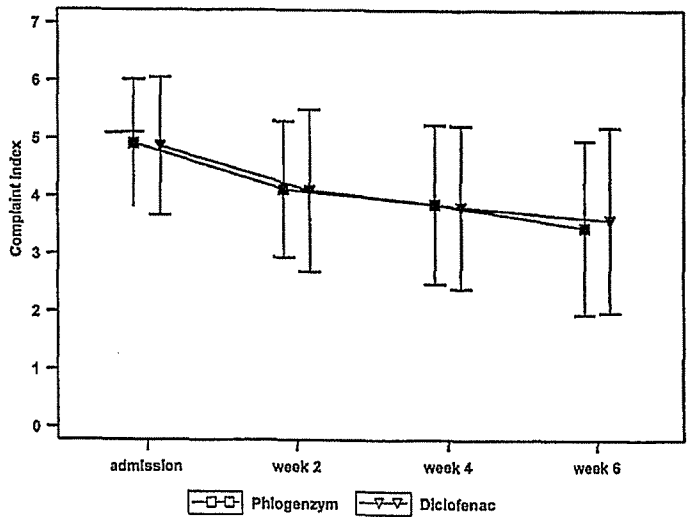


Fig. 2 Complaint Index: pain at rest and in motion; restricted function (VAS; cm), means and standard deviations, missing values replaced by LVCF

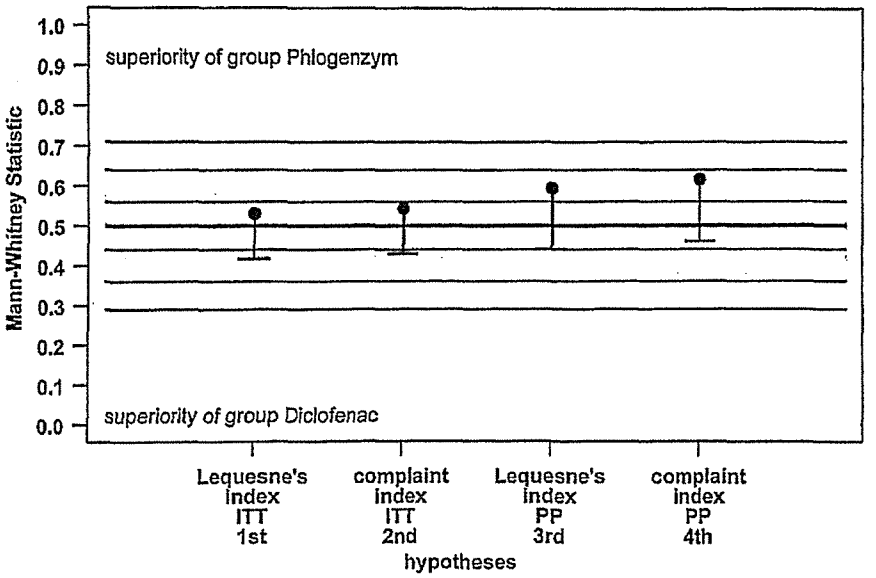
detected in any of the groups. For joint circumference of the more affected knee only minimal medium decreases were found in the ERC group (1.2%) and there was no median decrease in the diclofenac group.

The number of patients with adverse events did not differ substantially between treatment groups (ERC 14/51, 27.5%; diclofenac 12/52, 23.1%). No serious adverse event occurred in this study. There were no considerable group differences to be found concerning the number of patients with related adverse events. The most often reported related adverse events were diarrhea (ERC: 7/51, 13.7%; diclofenac: 7/52, 13.5%). In the ERC group five patients terminated the study early owing to adverse events (Table 2). In each case the event was of moderate severity, and in 4 patients was described as (possibly) related to the test drug. One patient reported diarrhea, edema and breathing difficulties after 2 weeks in the study, one patient reported epigastric burning after 1 week, one patient reported dryness of mouth, loss of appetite and heart sensations after 1 week, one patient reported numbness in the mouth and muscle spasms in the lumbosacral region after 1 week, and one patient reported hypopigmentation, rashes and acne after 5 weeks. The blind was not broken in any of these cases.

The counting of normal and abnormal laboratory values did not indicate any remarkable differences between the treatment groups, yet there were decreases in medians of SGOT, SGPT and γ-GT in the ERC group and increases in the diclofenac group.

Judgment on safety by investigator and by patient did not reveal noteworthy group differences. Safety was

Fig. 3 Efficacy criteria: LFI and Complaint Index (ITT and PP); percentage change from baseline; LVFC, at week 6; Mann–Whitney statistic and confidence interval for equivalence (97.5% CI, one-sided)



0.29 / 0.71 = large difference; 0.36 / 0.64 = medium sized difference; 0.44 / 0.56 = small difference; 0.5 = equal

judged as 'very good' or 'good' by most of the patients (ERC 33/37, 89.2%; diclofenac: 37/43, 86.0%) and physicians (ERC 32/38, 84.2%; diclofenac 37/43, 86.0%).

Discussion

In this randomized double-blind study all three domains – pain, function and global assessment by physician and patient – were covered, in accordance with recent recommendations for the evaluation of response in clinical trials on OA [14]. The LFI was used as a well-established tool for assessing efficacy in trials of OA of the knee. Our study supports the hypothesis that in patients suffering from a disease flare of OA of the knee with acute pain, ERC 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.

In this respect, the results obtained from this study confirm those observed in other trials [15, 16, 17] also demonstrating the efficacy of ERC in the treatment of painful episodes of OA of the knee. A large epidemiological cohort study gave evidence that in patients with rheumatic joint diseases, an even higher success rate of ERC treatment can be expected in total when compared with NSAIDs (mainly diclofenac) at comparable baseline and treatment situations [6].

Our study has a potential limitation in the fact that placebo control is lacking. We felt that for the first such trial in our country a comparison against a well-established standard such as diclofenac should be the initial step. External validation can be done by comparing the changes in efficacy parameters in our study with published data for similar studies with NSAIDs where a good agreement is observed. The fact that equal efficacy was proven for a broad range of parameters assessing pain and function speaks against a predominance of psychosomatic factors biasing the results obtained. Nevertheless, it is evident that a placebo-controlled trial is required. Such a trial may also address the question of longer treatment times, eventually evaluating an on-demand treatment regimen. The results from this epidemiological study indicate that ERC exhibits better safety and tolerability than NSAIDs. In our trial, in contrast to other similar studies, we found no difference in the safety/tolerability profile of the two treatments. In particular, the GI safety profile of both treatments did not differ substantially in the current study. One must bear in mind that with a power of 95% one would need 300 patients in order to observe one adverse event that occurs with a probability of 1% and 600 patients for adverse events that occurs with a probability of 0.5%. Thus, our study was not designed to demonstrate the superiority of ERC concerning gastrointestinal complications. Nevertheless, our study showed a trend towards an increase in liver enzymes under diclofenac therapy, which was not observed under ERC.

In summary, the current study is in line with other published data establishing that ERC is equally effective as NSAIDs in the treatment of painful OA with a disease flare. Onset of efficacy may be slower but the patients may profit from its well-known superior safety and tolerability profile. Thus ERC emerge as an alternative in the standard of care for OA, allowing more patients to be treated for longer periods without the inherent toxicities of NSAIDs.

Acknowledgements The authors are indebted to Dr V. W. Rahlfs, IDV, Gauting, Germany, for performing the statistical analysis. We are grateful to Dr Mehnaz Rashid, Pacific Pharmaceuticals Ltd, Lahore (Pakistan) for her advice and support in conducting this trial, and to Dr W. Schiess, Mucos Pharma, for helpful assistance in preparing this manuscript.

References

1. Pelletier JP, Martel_Pelletier J, Abramson SB (2001) Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 44:1237–1247
2. Pincus T (2001) Clinical evidence for osteoarthritis as an inflammatory disease. Curr Rheumatol Rep 3:524–534
3. Brooks P (1998) Use and benefits of nonsteroidal anti-inflammatory drugs. Am J Med 104:9S–13S; discussion 21S–22S
4. Roth SH, Bennett RE (1987) Nonsteroidal anti-inflammatory drug gastropathy. Recognition and response. Arch Intern Med147:2093–2100
5. Langman MJ, Weil J, Wainwright P et al. (1994) Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs [see comments] [published erratum appears in Lancet 1994 May 21;343 (8908):1302]. Lancet 343:1075–1078
6. Wittenborg A, Bock PR, Hanisch J, Saller R, Schneider B (2000) Vergleichende epidemiologische Studie bei Erkrankungen des rheumatischen Formenkreises am Beispiel der Therapie mit nichtsteroidalen Antiphlogistika versus einem oralen Enzymkombinationspräparat [comparative epidemiological study in patients with rheumatic diseases illustrated in an example of a treatment with non-steroidal anti-inflammatory drugs versus an oral enzyme combination]. Arzneim Forsch/Drug Res 50:728–738
7. Kelly GS (1996) Bromelain: a literature review and discussion of its therapeutic applications. Alt Med Rev 1:243–257
8. Klaschka F (1996) Oral enzymes—new approach to cancer treatment: immunological concepts for general and clinical practice; complementary cancer treatment. Gräfelfing: Forum-Med-Verl-Ges
9. Food and Drug Administration (1995) Labeling guidance diclofenac sodium delayed-release tablets.
10. US Department of Health and Human Services Food and Drug Administration (1998) Guidance for Industry: Clinical development programs for drugs, devices, and biological products intended for the treatment of osteoarthritis (OA), draft guidance, February 1998
11. Karbowski A, Schwitalle M, Eckardt A (1998) Oxaprozin versus diclofenac retard in treated of activated arthrosis. Zeitschri Rheumatol 57:108–113
12. Lequesne MG, Mery C, Samson M, Gerard P (1987) Indexes of severity for osteoarthritis of the hip and knee. Validation – value in comparison with other assessment tests [published errata appear in Scand J Rheumatol Suppl 1988;73:1 and Scand J Rheumatol 1988;17 (3):following 241]. Scand J Rheumatol Suppl 65:85–89

13. Colditz GA, Miller JN, Mosteller F (1988) Measuring gain in the evaluation of medical technology. The probability of a better outcome. Int J Technol Assessment Health Care 4:637–642
14. Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD (2000) Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. Osteoarthritis and Cartilage/Oars. Osteoarthritis Res Soc 8:395–403
15. Klein G, Kullich W (2000) Short-term treatment of painful osteoarthritis of the knee with oral enzymes. A randomised, double-blind study versus diclofenac. Clin Drug Invest 19:15–23
16. Singer F (1997) Phlogenzym in the treatment of a monoarticular gonarthritis – efficacy and tolerance, study no. MU-695 414. Geretsried: Mucos Pharma
17. Singer F, Singer C, Oberleitner H (2001) Phlogenzym versus diclofenac in the treatment of activated osteoarthritis of the knee. A double-blind prospective randomized study. Int J Immunother XVII :135–141