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Comparison of Aceclofenac with Diclofenac in the Treatment of Osteoarthritis

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Summary **A multicentre randomised, double-blind, parallel group, general practice study was undertaken to investigate the efficacy and safety of aceclofenac (200 patients, 100mg twice daily and placebo once daily) in comparison with diclofenac (197 patients, 50mg three times daily) in patients with osteoarthritis of the knee. The treatment period of twelve weeks was preceded by a washout period of two weeks duration. At end point, patients in both aceclofenac and diclofenac-treated groups exhibited significant improvement in pain intensity ($p=0.0001$). Although both treatment groups showed significant improvement in all investigators' clinical assessments (joint tenderness, swelling, pain on movement, functional capacity, overall assessment), there were no significant differences between the groups. There was, however, a trend towards greater improvement in complete knee movement and reduced pain on movement with aceclofenac. In patients with initial flexion deformity, aceclofenac was significantly more effective than diclofenac in improving knee flexion after 2-4 weeks of treatment. Patients' subjective assessment of pain relief demonstrated significantly greater efficacy with aceclofenac. At end point, 71% of patients in the aceclofenac group reported improvement in pain intensity as compared to 59% treated with diclofenac ($p=0.005$). Tolerability of aceclofenac was better than with diclofenac as fewer patients experienced gastrointestinal adverse events. In particular, the incidence of treatment related diarrhoea was less with aceclofenac (1%) than with diclofenac (6.6%). In summary, this study supports a therapeutic role for aceclofenac in arthritis and suggests that it is an alternative NSAID to diclofenac in the treatment of osteoarthritis.**

Key words **Aceclofenac, Nonsteroidal-Antiinflammatory Drugs, Diclofenac, Osteoarthritis, Efficacy, Safety**

INTRODUCTION

Osteoarthritis (OA), is a frequent cause of pain and disability in joints (1) particularly in the elderly. The natural cause of this chronic condition is not well understood (2). Generally, it has an insidious onset and a variable relationship of symptoms and functional impairment with slowly evolving pathological and radiographical changes. Current medical management is restricted to attempts to relieve symptoms and minimise disability.

Because of their analgesic and anti-inflammatory properties nonsteroidal anti-inflammatory drugs (NSAIDs) have long been the preferred therapy for relief of the pain and stiffness of arthritic diseases, including OA, although their use in this condition has been the subject of controversy (3). The inflammatory component of OA, for example, is relatively mild (4) which makes the use of NSAIDs questionable. More importantly, the threat of serious gastro-intestinal complications is a major concern of long term NSAID therapy (5). Nevertheless, NSAIDs are widely prescribed to reduce joint pain and stiffness in OA and numerous clinical trials have demonstrated their efficacy in pain relief (6,7).

Aceclofenac, a new NSAID, has recently been described as exhibiting good anti-inflammatory and analgesic efficacy in experimental animal models while maintaining better gastric tolerance in comparison with other NSAIDs, such as indomethacin and diclofenac (8). Indeed the therapeutic index for aceclofenac was reported to be four times greater than that of diclofenac.

Short term clinical studies have demonstrated the efficacy of aceclofenac in pain relief following dental ex-

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traction and episiotomy (9, 10), and in the chronic treatment of rheumatoid arthritis (11) and osteoarthritis (12). In some comparative studies, there was a tendency for aceclofenac to be better tolerated than diclofenac (12), with fewer patients being withdrawn from treatment due to gastric intolerance.

This paper describes a long term double-blind parallel group evaluation of the safety and efficacy of aceclofenac compared to an established NSAID (diclofenac) in patients with OA of the knee. In addition, the aim of this study was to confirm previous findings of improved gastric tolerance following aceclofenac administration as compared to diclofenac.

PATIENTS AND METHODS

A randomised, double-blind parallel, group evaluation carried out in 104 general practices and 2 outpatient clinics in the UK and Belgium was undertaken to investigate the efficacy and safety of aceclofenac in comparison with diclofenac in patients with osteoarthritis of the knee joint. The double-blind treatment period was preceded by a washout period of two weeks duration. The duration of double-blind treatment was 12 weeks.

Ethical committee approval was obtained from the Thames Valley Independent Ethics Committee and from the Committee for Medical Ethics of the OCMW in Antwerp, Belgium. Written informed consent was obtained from all eligible patients prior to entry.

Patients of either sex (age 18-75 years) with confirmed radiological and symptomatic OA of the knee of more than 3 months duration and a history of positive response to one or more NSAIDs in the previous year, were considered eligible for the study. OA was diagnosed on combined radiological and clinical grounds which included the presence of asymmetric joint space narrowing and at least one of the following: subchondral sclerosis, marginal osteophyte formation and/or subchondral pseudocysts with sclerotic walls. At least three of the following clinical criteria were to be present: pain on weight bearing, night pain, stiffness, pain at rest, lack of improvement in subject's opinion.

The exclusion criteria for the trial included: histories of renal, hepatic, cardiovascular disease or recent gastrointestinal disease or blood dyscrasias, current clinically significant anaemia, recent haemorrhage or alcohol or drug abuse; recent febrile viral infection or major surgery; treatment with anti-coagulant or oral hypoglycaemic drugs, previous hypersensitivity or other reaction to any NSAID, treatment with an investigational drug, intra-articular or parenteral steroids in the previous 4 weeks, pregnant or nursing females or those likely to be so, women of child-bearing age not using adequate contraception.

The initial screening assessment consisted of a full medical history and physical examination including both radiological and clinical verification of the disease. Blood and urine samples were taken for routine laboratory screens which included full blood count, plasma proteins, renal and hepatic function tests.

A total of 397 patients who satisfied all the selection criteria received either aceclofenac (aceclofenac group, 200 patients) or diclofenac (diclofenac group, 197 patients) according to a randomisation schedule. Paracetamol use (500mg, 1-2 tablets up to a maximum of 8 daily) was permitted on an as-required basis during the washout period and the first two weeks of the double-blind treatment period. During the double-blind treatment period patients received aceclofenac 100mg, twice-daily (bid) and placebo once-daily (lunch time), or diclofenac 50mg, three times daily (tid) for 12 weeks. Drugs that were being taken at the time of entry for concomitant disease, which did not constitute exclusions, were permitted. No other analgesics or anti-inflammatory agents were permitted during the trial.

Clinical efficacy assessments (by the investigator and patient), including measurement of vital signs, were undertaken on inclusion into the study and were repeated at 2, 4, 8 and 12 weeks thereafter. Laboratory safety parameters were monitored at 2, 4 and 12 weeks after the start of the study. The physical examination was repeated at the final evaluation (week 12).

The major efficacy criterion was the investigators' assessment of the intensity of joint pain at rest and was recorded as a pain score according to a 5-point scale with low scores associated with less pain.

Additional variables measured by the investigator were joint tenderness, joint effusion, erythema (redness of skin over the joint), and the degree of pain on movement. One function (e.g. walking or climbing stairs) was selected at the beginning of the study and used to assess the degree of disability or interference caused by the OA, and an overall assessment of the subject's current condition was recorded. All these assessments were made on 5-point scales with low scores being associated with less pain. Knee flexion was measured by passive movement using a goniometer and recorded in degrees. If the knee could be straightened then the flexion was measured from the zero position; however, if the knee could not be straightened, the starting position was recorded as the initial flexion deformity and was subsequently measured in degrees from the theoretical zero position.

Each subject recorded duration of stiffness, night pain, pain intensity at rest and weight-bearing pain, which was that experienced during selected activity (ies), as well as

an overall assessment of his/her condition. All these assessments were made on a 5-point scale with low scores being associated with less pain.

The nature of any adverse event was recorded using WHO code terms at each visit, and the investigator gave his/her opinion as to the relationship with treatment. A count of returned tablets was made to check compliance.

The results were analysed using SAS software. All statistical tests were two-sided and a probability of 0.05 was set as the minimum level of significance. Comparability of treatment groups (demographic and baseline characteristics) were analysed using Student's two sample t-test and chi-squared test as appropriate.

Efficacy variables were summarised and analysed using three methods:

- *Intention-to-treat analysis.* This analysis included all patients who had received at least one dose of study treatment for whom efficacy data were available.
- *Per protocol analysis.* This analysis included all patients except protocol violators and poor compliers.
- *Endpoint Analysis.* This analysis included all patients in the intention-to-treat cohort using the last observation carried forward technique; data from the last evaluation visit were used in the analysis.

Statistical methods performed were either the Wilcoxon two sample test, the Mantel-Haenszel chi-square test or the chi-square test as appropriate. The number of patients with adverse events was compared using chi-square or Fisher's exact tests as appropriate. All laboratory and vital signs data were assessed and analysed using the chi-square and the Wilcoxon-two sample tests respectively.

RESULTS

Patient characteristics

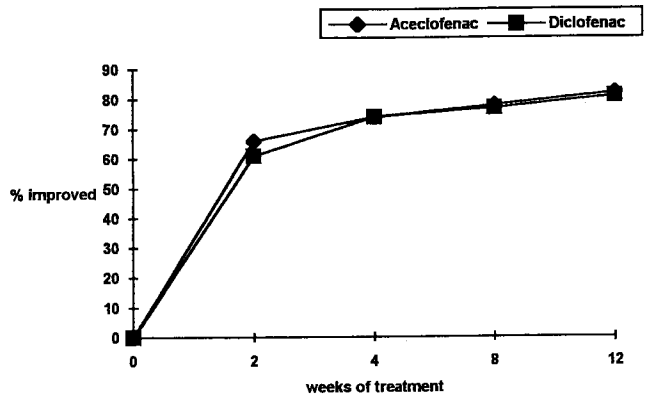
A total of 462 patients were enrolled of whom 397 patients were randomized and received treatment. Two hundred subjects received aceclofenac 100mg bid and 197 received diclofenac 50mg tid. The demographic parameters (Table I) and medical histories were comparable for each group.

A total of 261 patients (138 (69%) on aceclofenac and 123 (62%) on diclofenac) completed the study. The differences between the groups in the number of patients completing the study (p=0.17) were not statistically significant. The most common reasons for withdrawal in each group were adverse events (25 in the aceclofenac group and 32 in the diclofenac group) and protocol violation (12 in the aceclofenac group and 18 in the diclofenac group). Nine patients in each group were withdrawn due to deterioration of their condition.

Table I: *Demographic characteristics*

	Aceclofenac (n=200)	Diclofenac (n=197)
Male: female	81:119	92:105
Age[a], years	62.4±7.8	60.9±9.0
Weight[a], kg	79.7±15.1	81.1±15.8
Height[a], cm	164.9±8.9	165.7±8.8

[a] Values are means ± SD



n (AC)	198	124	126	120	115
n(DC)	193	113	127	114	103

Fig. 1: Mean percentage improvement in investigator's assessment of pain intensity by intention-to-treat analysis at each study visit. At all visits, statistically significant improvement over baseline (p=0.0001) was observed in both groups; no significant differences were observed between groups at any visit. The number of patients improved in each group at each visit and the number of patients assessed at baseline are given.

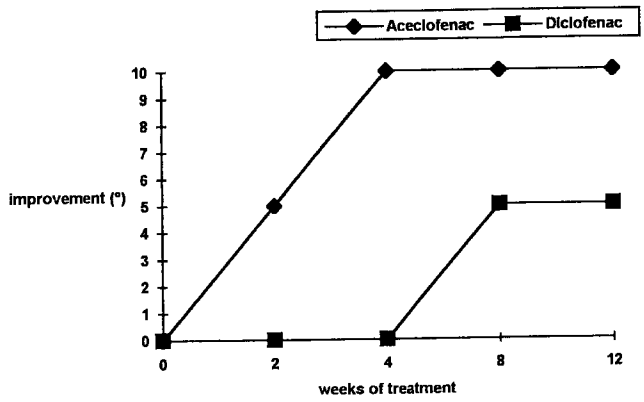
Efficacy

All 397 patients who were randomised and received at least one dose of the study drug were included in the intention-to-treat efficacy analyses. A total of 146 patients, 65 in the aceclofenac group and 81 in the diclofenac group, were excluded from the per protocol analysis for the following reasons: abnormal renal function tests (27), noncompliance (18), took paracetamol (71) or NSAID during study (10), concurrent condition not permitted by the protocol (6), violated protocol in another way (40).

The primary efficacy variable was the investigators assessment of pain intensity at rest. In both treatment groups, a statistically significant decrease in pain from baseline was observed by intention-to-treat analysis (Fig. 1). However, there were no statistically significant differences between groups at any visit. At end-point, 143 (74.5%) patients in the aceclofenac group and 131 (70.4%) in the diclofenac group had an improvement in

Table II: *Change in investigators' assessments other than knee flexion, from baseline to endpoint*

Categorical assessments	Change from baseline				p-value
	Aceclofenac		Diclofenac		
	no.	% patients	no.	% patients	
Pain intensity	192		186		
improved		74.5		70.4	0.40
no change		21.9		25.3	
deteriorated		3.6		4.3	
Joint tenderness	192		186		
improved		72.4		66.7	0.16
no change		25.0		28.5	
deteriorated		2.6		4.9	
Swelling	192		186		
improved		58.3		53.8	0.21
no change		39.1		40.9	
deteriorated		2.6		5.4	
Erythema	192		186		
improved		23.4		18.8	0.14
no change		75.0		77.4	
deteriorated		1.6		3.8	
Pain on movement	188		180		
improved		70.2		62.8	0.093
no change		23.9		27.8	
deteriorated		5.8		9.4	
Functional capacity	192		186		
improved		74.0		71.0	0.50
no change		23.4		25.8	
deteriorated		2.6		3.2	
Overall assessment	192		186		
improved		74.5		69.9	0.18
no change		23.4		25.3	
deteriorated		2.1		4.8	



p (AC vs DC)		0.0004	0.04	NS	NS
n (AC)	53	43	39	33	29
n (DC)	52	43	39	35	29

Fig. 2: Median increases in movement (in degrees) on knee flexion in patients with initial flexion deformity by intention-to-treat analysis at each study visit. At all visits, except at 2 weeks in the diclofenac group, statistically significant improvement over baseline ($p < 0.005$) was observed in both groups. Significant differences between groups at 2 and 4 weeks are indicated. The number of patients showing increases in movement in each group at each visit and the number of patients assessed at baseline are given.

pain intensity. Each treatment gave a significant improvement from baseline to end point ($p=0.0001$) although no difference was detected between the treatments.

While in both treatment groups significant improvements in all the investigators' clinical assessments (joint tenderness, swelling, erythema, pain on knee movement, functional capacity, overall assessment) were observed (Table II), there were no statistically significant differences between the groups for the change in any variable from baseline to endpoint. The same was also true for knee flexion from the zero position which increased 7.0° from baseline to end point in the aceclofenac group and 5.0° in the diclofenac group ($p=0.20$).

In evaluating data from patients with initial flexion deformity, the intention-to-treat analysis showed a statistically significant difference between the treatment groups in the change from baseline at weeks 2 and 4 (Fig. 2).

Aceclofenac treatment improved knee flexion over baseline at all time points. At endpoint, though, median increases under aceclofenac (10°) and diclofenac (1°) did not differ significantly ($p=0.12$). The overall data for complete knee movement for all patients (adjusted for initial flexion deformity) approached statistical significance in favour of aceclofenac (10° increase) in comparison to diclofenac (5° increase), although the results (median) failed to reach significance ($p=0.088$).

Each treatment also produced significant improvements from baseline in all patients' assessments. Table III describes the changes in patients' assessments from baseline to end point. While activity pain and global evaluation did not differ between groups, there was a highly significant difference between the groups in the change in pain intensity in favour of aceclofenac ($p=0.005$), and a trend towards a greater improvement in night pain with aceclofenac than with diclofenac ($p=0.098$). Duration of stiffness did not differ significantly ($p=0.26$) between groups, the median decreases being 9 min with aceclofenac and 7 min with diclofenac. Paracetamol use was significantly less in the aceclofenac group (median 14 tablets) than in the diclofenac group (22 tablets) at week 2 ($p=0.043$).

Table III: *Change in patients' assessments from baseline to endpoint*

Assessments	Change from baseline (% patients)		p-value
	Aceclofenac	Diclofenac	
Activity pain			
improved	78.0	72.0	0.28
no change	17.8	23.7	
deteriorated	4.2	4.3	
Night pain			
improved	65.1	57.0	0.098
no change	29.7	35.5	
deteriorated	5.2	7.5	
Pain intensity			
improved	71.4	59.1	0.005
no change	24.5	31.2	
deteriorated	4.2	9.7	
Global evaluation			
improved	77.1	69.9	0.18
no change	17.7	24.2	
deteriorated	5.2	5.9	

Table IV: *Adverse events possibly related to treatment, which occurred in at least three patients in either group*

Adverse event per body system	No of patients (%)			
	Aceclofenac		Diclofenac	
Gastrointestinal				
abdominal pain	5	(2.5)	7	(3.6)
constipation	1	(0.5)	5	(2.5)
diarrhoea	2	(1.0)	13	(6.6)
dyspepsia	5	(2.5)	6	(3.1)
epigastric pain (not food related)	3	(1.5)	6	(3.1)
flatulence	4	(2.0)	2	(1.0)
heartburn	9	(4.5)	11	(5.6)
indigestion	12	(6.0)	11	(5.6)
nausea	6	(3.0)	6	(3.1)
vomiting	2	(1.0)	4	(2.0)
Liver and biliary				
gamma GT increased			4	(2.0)
AST increased	2	(1.0)	4	(2.0)
ALT increased	2	(1.0)	3	(1.5)
Metabolic and nutritional				
creatinine increased	4	(2.0)		
Body as a whole-general				
headache	4	(2.0)	8	(4.1)
tiredness	3	(1.5)	1	(0.5)

Safety and adverse events

During active treatment, 195 adverse events were reported by 103 (52%) patients in the aceclofenac group and 211 events were reported by 101 (51%) patients in the diclofenac group. There was no difference in the proportion of patients reporting adverse events ($p=0.96$) and no difference in the number of events experienced ($p=0.34$).

Indigestion was the most frequently reported adverse event in the aceclofenac group (6% of patients), whereas 10% of patients in the diclofenac group complained of diarrhoea and heartburn and indigestion were reported by 6% each. The profile of most frequently reported adverse events was comparable between the two groups with disorders of the gastrointestinal system, nervous systems and special senses, and the body as a whole. However, there was a higher frequency of gastrointestinal events, particularly diarrhoea, in the diclofenac group (106 events) than in the aceclofenac group (79 events). In total, 104 events (in 64 patients) reported in the aceclofenac group and 127 events (in 72 patients), reported in the diclofenac group were considered to be at least possibly drug-related. Of these 59 (aceclofenac group) and 83 (diclofenac group) were gastrointestinal intolerance. The most frequently related events are listed in Table IV.

In patients who withdrew from the study because of adverse events, 16 patients in the aceclofenac group and 23 in the diclofenac group did so because of events at least possibly related to the medication. There was one death in the aceclofenac group which was considered unrelated to the study drug. Postmortem findings indicated that the cause of death was subarachnoid haemorrhage due to a ruptured cerebral aneurism.

Six patients in the aceclofenac group and 13 patients in the diclofenac group had clinically significant changes in laboratory parameters which resulted in the withdrawal of the drug. These changes were reported as adverse events for 4 patients in the aceclofenac group and 8 patients in the diclofenac group. The majority of cases involved changes in serum creatinine and liver function tests.

DISCUSSION

Diclofenac is internationally well-established as a symptomatic therapy for OA and is similar in efficacy to other NSAIDs (13). The results of the present comparative study of aceclofenac and diclofenac in OA, confirm the efficacy of aceclofenac, showing that significant improvements in all efficacy variables are obtained with both treatments, but for the majority of variables, no significant differences were seen between aceclofenac and diclofenac groups during treatment.

There was both objective (assessment of knee flexion) and subjective evidence (patients' assessment of pain intensity) that aceclofenac was more effective than diclofenac. Indeed, aceclofenac was found to improve

knee flexion in patients who could not straighten their knees (initial flexion deformity) at all time points, only reaching statistical significance at weeks 2 and 4 of the study, while complete knee flexion in all patients was similar in both groups. There was also a trend suggesting greater improvement in pain on movement with aceclofenac than with diclofenac.

The time course of the improvement in knee flexion in patients with initial deformity indicates that the onset of action of aceclofenac was more rapid than that of diclofenac. This may be related to the fact that concentration of aceclofenac in the joint tends to be greater with aceclofenac than with diclofenac (14).

Patients' assessment of pain relief also demonstrated significantly greater efficacy with aceclofenac. At endpoint, 71% of patients in the aceclofenac group reported improvement in pain intensity as compared to 59% in the diclofenac group. (It should be noted, however, that pain at rest in patients with OA is dependent on a variety of subjective factors and can be inconsistent). In addition, global evaluation of their condition suggested a greater improvement with aceclofenac than with diclofenac. The fact that, at week 2, patients in the aceclofenac group required significantly less escape medication with paracetamol than did patients in the diclofenac group, further supports the more rapid onset of action of aceclofenac.

Safety and tolerability are important factors in NSAID therapy. This study has demonstrated that aceclofenac is well tolerated by patients and indeed the results indicate that gastrointestinal tolerability may be more favourable with aceclofenac than with diclofenac. Overall there were fewer gastrointestinal adverse events which were considered drug-related to aceclofenac (59 events) than to diclofenac (83 events). In particular, the incidence of treatment-related diarrhoea was less with aceclofenac (1%) than with diclofenac (6.6%) and constipation was less frequent. These data tend to support in patients the findings of a previous study in healthy volunteers suggesting that aceclofenac is associated with better gastrointestinal tolerance than diclofenac (15).

The ultimate aim in management of OA is to provide the patient with effective and well-tolerated drugs to minimize symptoms which will improve their quality of life. Based on the data from this study, aceclofenac is as effective as diclofenac in relieving arthritic pain and indeed may be better or faster-acting on parameters such as knee flexion and subjective pain assessment. Tolerability of aceclofenac was very good and there was some evidence that the incidence of certain gastrointestinal adverse effects was lower than for diclofenac. Since NSAID-induced gastropathy is particularly significant for OA patients who rely on long term NSAID therapy, a drug with increased gastric tolerance would provide a significant cost effective therapeutic option in the treatment of OA.

In summary, the results from this study have confirmed a therapeutic potential of aceclofenac in arthritis and suggest an alternative NSAID to diclofenac in the treatment of osteoarthritis.

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REFERENCES

1. Felson, D.T. Osteoarthritis. Rheum Dis Clin North Am 1990, 16, 499-512.
2. Dieppe, P., Cushnaghan, J. The natural course and prognosis of osteoarthritis. In: Osteoarthritis: diagnosis and medical surgical management. Eds.: Moskowitz, R.W. et al. Philadelphia: WB Saunders, 1992, 399-412.
3. Brooks, P.M., Potter, S.R., Buchanan, W.W. Non-steroidal anti-inflammatory drugs and OA: help or hindrance? J Rheumatol 1982, 9, 3-5.
4. Peyron, J. Inflammation in osteoarthritis (OA): Review of its role in the clinical picture, disease progress, subsets and pathology. Semin Arthritis Rheum 1981, 11 (suppl 1), 115-119.
5. Roth, S.H., Bennet R.E. Nonsteroidal anti-inflammatory drug gastropathy. Arch Intern Med 1987, 147, 2093-2100.
6. Brandt, K.D. Osteoarthritis: treatment guidelines. Drug Therapy 1988; 18: 26-40.
7. Al Arfag, A., Davis, P. Osteoarthritis 1991. Current drug treatment regimens. Drugs 1991, 41, 193-201
8. Grau, M., Montero, J.L., Guasch J, Felipe, A., Carrasco, E., Julia, S. The pharmacological profile of aceclofenac, a new nonsteroidal anti-inflammatory and analgesic drug. Agents Actions Suppl 1991, 32, 125-129.
9. Sainz Olalla, F. Analgesic efficacy of aceclofenac. Double-blind study vs placebo in the treatment of odontalgia. Curr Ther Res 1989, 43, 900-902.
10. Movilia, P.G. Evaluation of the analgesic activity and tolerability of aceclofenac in the treatment of post-episiotomy pain. Drugs Exp Clin Res 1989, 15, 47-51.
11. Giorgianni, G., Ottaviani, C., Soliano, A., Campi, N. Efficacy and tolerability of aceclofenac versus ketoprofen in the treatment of rheumatoid arthritis. Curr Ther Res 1992, 51, 175-184
12. Diaz, C., Rodriguez, A., Geli, C., Llobet, J.M., Tapounet, R. Comparison of aceclofenac and diclofenac in osteoarthritic pain. Curr Ther Res 1988, 44, 252-256.
13. Altman, R. International experiences with diclofenac in osteoarthritis. Am J Med 1986, 80 Suppl 45, 48-52.

14. Cecchettin, M., Cerea, P., Torri, G. Therapeutic efficacy of aceclofenac and diclofenac in acute knee arthroses. A study of E_2-prostaglandin levels in synovial fluid and in serum. Clin Trials J 1988, 25, 144-151.
15. Wassif, W., Bjarnason, I. A comparison of the effects of aceclofenac and diclofenac on gastrointestinal blood loss. Br J Clin Res 1992, 3, 109-114.[1]

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