Aceclofenac is a Well-tolerated Alternative to Naproxen in the Treatment of Osteoarthritis

D. KORNASOFF, H. FRERICK, J. BOWDLER, E. MONTULL

Summary **The efficacy and safety of aceclofenac (100 mg bid), a new nonsteroidal anti-inflammatory/anti-rheumatic agent, were compared with those of naproxen (500 mg bid) in a multi-centre, twelve-week, randomized, double-blind, parallel-group clinical trial in outpatients with active osteoarthritis of the knee. 190 patients received aceclofenac, 184 naproxen.**

The two treatments were compared on the basis of several characteristic clinical features of osteoarthritis of the knee, including various pain measurements. In both groups, the treatment resulted in a significant reduction of the pain at rest, pain on movement and the pain from pressure on the joint, 76-86% of aceclofenac patients reporting reduction in pain after 12 weeks. Three-quarters of the aceclofenac-treated patients had an accompanying reduction in joint swelling and 81.4% in knee function capacity, up to complete freedom of movement. Joint stiffness, which at baseline lasted 20 minutes, was reduced in the aceclofenac group to 10 minutes. A statistically significant difference in the efficacy of the two drugs was not found. The 34 adverse drug effects documented in 24 (12.6%) of the aceclofenac patients were fewer than the 43 events in 30 patients (16.3%) reported for naproxen. The trend towards better tolerability of aceclofenac manifested itself above all in a lower total incidence of gastrointestinal side-effects.

Aceclofenac is as effective as naproxen in the symptomatic treatment of osteoarthritis of the knee and is well tolerated in general.

Key words **Aceclofenac, Naproxen, Osteoarthritis, Pain.**

INTRODUCTION

Aceclofenac, 2-[2,6-dichlorophenyl) amino] phenylacetoxy acetate, is a new nonsteroidal anti-inflammatory drug (NSAID) with antiinflammatory, antipyretic and analgesic properties (1). In experimental studies, aceclofenac was similar in potency to indomethacin and diclofenac and superior to naproxen, but its lower incidence of gastrointestinal side effects resulted in a therapeutic index which was higher than that of both diclofenac and naproxen (1).

Aceclofenac is well tolerated and effective in the short and longterm treatment of articular pain and rheumatoid arthritis (2-8). In osteoarthritis, aceclofenac has proved to be at least as effective as diclofenac in improving symptomatology and tends to be better tolerated (9-12). Clinical trials in patients with acute knee pain with synovial effusion have shown that aceclofenac in synovial fluid and in serum can induce a significant decrease in prostaglandin E_2 levels (2). The inflammatory component of osteoarthritis, however, tends to be mild and NSAIDs are viewed more as analgesics in this condition (14). Naproxen is a widelyused, well-tolerated NSAID which shows good analgesic efficacy in osteoarthritis (15).

The following is a report of the results of a 12-week, randomized, double-blind clinical trial carried out to compare the efficacy and safety of aceclofenac with that of naproxen in patients with active osteoarthritis of the knee.

PATIENTS AND METHODS

Patients

The study was multi-centre (31 centres in Germany, 9 in France), randomized, double-blind clinical trial comparing two parallel treatment groups and was conducted in accordance with the Guidelines for Good Clinical Practice (GCP) and with the Declaration of Helsinki. In-

Medical Department, Prodesfarma Research Centre, Sant Just Desvern (Barcelona), Spain.

cluded in the study were male and female out-patients aged 18 to 75 years who gave their written informed consent and who had had clinically confirmed and radiologically verified osteoarthritis of the knee (defined as asymmetric joint space narrowing and at least one of subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls) for at least three months. The clinical inclusion criteria for each patient were, among others, the presence of at least three of the following clinical symptoms: functional pain, nocturnal pain and pain at rest with a rating of 3 on a scale of 5 (low scores = less pain), a duration of joint stiffness of 10 minutes upon getting up or after a longer period of inactivity, as well as a rating of 3 on a scale of 5 for the patient's own assessment of his or her disease. In keeping with the criteria of disease duration, each patient had to have a documented medical history of a therapeutic response to NSAIDs (including aspirin) within the previous year. Exclusion criteria included inflammatory bowel disease, active gastrointestinal ulcers, gastrointestinal bleeding, serious hepatic disorders or kidney dysfunction, blood disorders, asthma and/or alcohol or drug abuse. Not included in the clinical trial were patients who were receiving anti-coagulants, barbiturates, sulphonylureas, diuretics or ACE inhibitors. Also excluded from participation were pregnant women and females of child-bearing age not using adequate contraception as well as patients with a known sensitivity or allergy to other NSAIDs or other analgesic drugs.

Based on previous placebo-controlled studies of similar NSAIDs, in which the physician's assessment of pain was the primary efficacy variable, a sample size of 150 per treatment group was considered sufficient to detect a difference between groups of approximately 10% at the 5% significance level with a power of 80%.

Treatment

The selected and randomized patients, who met all of the initial inclusion criteria during the fourteen day examination period preceding the start of the study, then started taking their assigned medication of either 100 mg aceclofenac or 500 mg naproxen. They were instructed to take two tablets daily: one tablet orally along with a liquid or food upon rising and a second tablet approximately twelve hours after the first dose for the total trial period of 12 weeks. During the wash-out phase and the first two weeks of treatment, patients were permitted to take one or two paracetamol tablets (500 mg) up to a maximum of four times daily as needed, but no other analgesically effective drug. Patients who had started physical therapy before entering the study were permitted to continue with it. Patients who relied on walking devices such as canes or crutches could continue to use them. Any changes in the physical therapy routine or in the use of the walking aid during the duration of this study were to be noted in the protocol.

Study procedure

The primary efficacy variable was the investigators' assessment of pain. The investigators examined the affected joint and assessed the following clinical parameters at baseline and at the end of the 12 week treatment period: pain on pressure, joint swelling, joint erythema, pain on movement as well as pain at rest and functional capacity. The event or degree of the symptoms was documented on scales of 1 to 5 with low scores being associated with fewer symptoms, as described previously (12). 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. Knee flexion in degrees, was measured in supine position with a goniometer. The investigators also made an assessment of the subject's current global condition. The patient's own assessment included a self-assessment of the pain intensity experienced in performing a selected activity or activities, the nocturnal pain and the pain at rest, the global assessment of their condition on a scale of 1 to 5, with low scores being associated with fewer symptoms, as well as the duration of joint stiffness after a period of inactivity such as sitting. The patients' responses to direct questions and their voluntary and spontaneous comments as to the adverse events were documented over the entire period of the trial. Included were their type, degree, duration, number and their connection with the tested treatment. Laboratory tests, including blood chemistry and urine analysis were completed at baseline and after 2, 4 and 12 weeks and vital sign checks, such as blood pressure and pulse were measured and included as part of the safety evaluation at baseline and after 2, 4, 8 and 12 weeks. Any changes in other medication or any other accompanying illness were documented and compliance check on the remaining tablets was also made.

Statistical analysis

Data not following a normal distribution were analysed using Fischer's exact test or chi-squared test (demographic data), the Wilcoxon test (continuous efficacy data) or Mantel-Haenszel chisquared test (categorical efficacy data) as appropriate. Normally distributed data

Table I: *Demographic characteristics of the patients (intention-to-treat analysis)*

	Aceclofenac	Naproxen
Number of subjects	190	184
Males	71	63
Females	119	121
Median age	61.0	61.5
IQ range (years)	55-69	54-69
Median weight	74.4	75.0
IQ range (kg)	70-84	69-84
Mean height	166.7	167.3
± SD (cm)	8.9	8.7
Median diastolic BP	84	82
IQ range (mmHg)	80-90	80-90
Median systolic BP	142	140
IQ range (mmHg)	130-150	130-150

IQ: interquartile range. No significant differences between groups.

were analysed using Student's t-test. The efficacy data were analyzed on an intention-to-treat basis, that is, the data from all randomized patients who took at least one tablet of trial medication were analyzed. Patients who failed to complete the trial and protocol violators were excluded in the per protocol analysis. In addition, an end point analysis was performed and included the data for all patients from their final visit regardless whether they had completed the twelve weeks of treatment. All analyses were produced on SAS. A probability of 0.05 was set as the minimum level of significance.

RESULTS

Patient characteristics

Of the 382 patients selected for the study, 374 were assigned at random to one of the two study groups. 190 patients received aceclofenac and 184 patients received naproxen as the trial medication (Table I). There were no significant differences between the two patient groups with regard to medical history on baseline clinical parameters. Recent past medication – in most cases diclofenac – was documented for 66 patients or 35% of the aceclofenac group and 69 patients or 38% of the naproxen group. Forty-three percent of the aceclofenac patients and 40% of the naproxen patients continued to receive concurrent medication for other illnesses.The most common concurrent condition, which was diagnosed in one quarter of the patients, was hypertension. Twenty-two patients or 12.5% of the aceclofenac group and 18 patients or 10.7% of the naproxen group also received physical therapy. Four of the patients in the aceclofenac and 2 of the patients in the naproxen group required a walking aid at the beginning of the trial and 3 of the patients in the aceclofenac and 4 of the patients in the naproxen group required a walking aid at the end.

Table II: *Summary of subject accountability*

	Aceclofenac	Naproxen
Received study treatment	190	184
Completed	145	135
Withdrawn*	45	49
Deterioration	8	4
Adverse event	5	10
Did not return	4	4
Free of symptoms	21	23
Protocol violators	1	2
Other	6	6

* Some patients withdrew for more than one reason.

Three hundred and seventy-four patients were included in the intention-to-treat analysis (Table II). There were 42 protocol violators who were not included in the per protocol analysis, 13 of whom did not exhibit disease at baseline. Approximately the equivalent number of patients in each group completed the study: 145 patients or 76.3% in the aceclofenac group and 135 patients or 73.4% in the naproxen group. The main reason for premature withdrawal in both groups was the complete relief of symptoms.

Compliance (tablet count) was excellent in both groups with 99% of the patients having taken the dispensed medication.

Efficacy

With the noted exceptions, the following data are based on the intention-to-treat analysis. No significant difference was found between the groups for this or any of the subsequent per protocol and end point analyses. The statistical evaluation indicated that there was no significant difference in the compared efficacy of the two drugs.

Investigator's assessment of pain on pressure, on movement and at rest

Upon their admission to the trial, the majority of the patients (> 90%) in both treatment groups had moderate to severe pain in the affected knee joint. Over the 12-week-course of the trial, their number decreased continuously. Between 76 and 86% of the patients showed an improvement in joint tenderness, pain on movement and pain at rest from pretreatment to the last assessment of the trial. Deterioration occurred in only 3% of the cases at most (Table III). The patients' own assessment of pain on movement and at rest was consistent

Table III: *Changes in efficacy criteria from pretreatment to end point (end point analysis). Investigator's assessments.*

Efficacy criteria Investigator's assessements	Aceclofenac no.	Aceclofenac % patients	Naproxen no.	Naproxen % patients
Joint swelling	189		181	
Deteriorated		1.6%		2.8%
No change		25.4%		22.1%
Improved		73.0%		75.1%
Joint erythema	189		181	
Deteriorated		0.5%		1.1%
No change		56.1%		51.4%
Improved		43.4%		47.5%
Functional capacity	188		180	
Deteriorated		0.5%		0.6%
No change		18.1%		15.6%
Improved		81.4%		83.9%
Joint tenderness on pressure	189		181	
Deteriorated		1.6%		2.2%
No change		16.4%		12.2%
Improved		82.0%		85.6%
Pain on movement	187		180	
Deteriorated		2.1%		1.1%
No change		14.4%		12.8%
Improved		83.4%		86.1%
Pain at rest	189		181	
Deteriorated		3.2%		1.7%
No change		20.6%		16.6%
Improved		76.2%		81.8%

No significant differences between groups.

Table IV: *Changes in efficacy criteria from pretreatment to end point (end point analysis). Subject's assessments.*

Efficacy criteria Subject's assessments	Aceclofenac no.	Aceclofenac % patients	Naproxen no.	Naproxen % patients
Weight bearing activity pain	187		179	
Deteriorated		1.6%		0.5%
No change		14.4%		16.2%
Improved		84.0%		83.2%
Night pain	187		178	
Deteriorated		3.7%		3.4%
No change		20.3%		17.4%
Improved		75.9%		79.2%
Pain at rest	188		180	
Deteriorated		4.8%		2.2%
No change		19.7%		15.0%
Improved		75.5%		82.8%
Overall assessment	189		181	
Deteriorated		3.2%		4.4%
No change		24.9%		23.2%
Improved		72.0%		72.4%
Change in duration of stiffness (minutes)	188		180	
Median		−10		−13
Interquartile range		(−12 to −5)		(−20 to −5)

No significant differences between groups.

with the investigators' assessment (Table IV). Nocturnal pain and the associated discomfort was decreased in 76% of the patients in the aceclofenac and 79% of the patients in the naproxen group.

Joint swelling

Mild to moderate swelling of the joint was noted in 78% of the patients in the aceclofenac and 84% of the patients in the naproxen group at the beginning of the trial.

Approximately three-quarters of the affected patients in both groups responded to the treatment (Table III). There was no change in the status or condition of 48 patients (25.4%) of the aceclofenac group and of 40 patients (22.1%) of the naproxen group.

Joint erythema

With the exception of 1 patient in the aceclofenac group, who had intense joint erythema at baseline, only 91 of 189 patients in the aceclofenac group and 92 of 181 patients in the naproxen group exhibited faint to moderate erythema at baseline. No statistically significant difference between groups was detected at any of the assessment visits. At end point, one patient or 0.5% of the aceclofenac group showed deterioration whereas 106 of the patients or 56.1% of the aceclofenac group showed no change compared with pretreatment. Improvement was documented in 82 of the patients or 43.4% of the aceclofenac group. Similar results were reported for the naproxen treated group (Table III).

Functional capacity

The anti-inflammatory component of the treatment in both groups resulted in an improvement of functional capacity. Improvement from the pretreatment value was noted in 81.4% of the aceclofenac patients and in 83.9% of the patients in the naproxen group (Table III). The objective improvement in knee function capacity can be seen in Table V.

Duration of joint stiffness

The initial or pretreatment median value of 20 minutes of joint stiffness after a set period of inactivity was reduced by 10 minutes in the aceclofenac and by 13 minutes in the naproxen group at end point. The improve-

Table V: *Knee flexion. Change from pretreatment. (Intention-to-treat analysis; Mean ± SD; *p < 0.05; t-test). Numbers of patients are given in brackets.*

	Aceclofenac		Naproxen	
	Pretreatment	Week 12	Pretreatment	Week 12
Knee flexion (°) (from zero position)	86.7 ± 25.8 (107)	*96.8 ± 21.1 (89)	88.7 ± 24.5 (96)	*99.8 ± 21.3 (81)
Knee flexion (°) (with initial deformity)	90.0 ± 25.2 (82)	*102.0 ± 17.1 (32)	87.3 ± 27.4 (85)	*96.7 ± 25.4 (39)
Total knee flexion (°)	81.7 ± 26.8 (189)	*95.5 ± 20.2 (48)	82.4 ± 26.3 (179)	*96.2 ± 21.7 (141)

ments from baseline within each group were statistically significant (p=0.001; Wilcoxon test).

Overall assessment of the condition

The investigators noted, as early as 2 weeks after the start of treatment, an improvement in the condition of 55.6% of the patients treated with aceclofenac and in 48.1% of the naproxen patients compared to pretreatment. After 12 weeks an improvement was documented in 73% of the aceclofenac patients and in 68.5% of the patients in the naproxen group. In the aceclofenac group, a deterioration was seen in 2.7% and no change in 24.3% of patients; in the naproxen group, the respective figures were 2.8% and 28.7%. The overall assessment by the patients did not differ statistically from that of the attending physicians (Table IV).

Safety and adverse events

The safety evaluation was based on the documented adverse events and their analysis as well as on the results of the laboratory tests and the recorded values for the vital signs. No clinically relevant changes in the vital signs (pulse and blood pressure) were found in either of the two treatment groups.

During the treatment period, 28 patients in the aceclofenac group reported 45 adverse events while 40 patients in the naproxen group reported 55 adverse events. Significantly more adverse events were recorded in the naproxen group than in the aceclofenac group (p = 0.025; Chisquared test). Thirty-four of the adverse events reported by the aceclofenac group and 43 of the adverse events in the naproxen group were at least possibly related to the medication (Table VI). The most commony reported adverse events (19 and 36 for aceclofenac and naproxen respectively) were those affecting the gastrointestinal tract. Six patients or 3.2% of the aceclofenac group and 7 patients or 3.8% of the naproxen group complained of stomach pain and 5 patients in each group complained of nausea.

Table VI: *Adverse events at least possibly related to study treatment. Number (%) of subjects.*

Body system	Preferred Term	Aceclofenac	Naproxen
Skin and appendages	Itching	1 (0.5%)	1 (0.5%)
Central and peripheral nervous system	Vertigo	2 (1.1%)	1 (0.5%)
Gastro-intestinal	Abdominal discomfort	1 (0.5%)	2 (1.1%)
	Abdominal pain	6 (3.2%)	7 (3.8%)
	Bloating	0	2 (1.1%)
	Constipation	0	2 (1.1%)
	Diarrhoea	2 (1.1%)	2 (1.1%)
	Epigastric not food related pain	0	2 (1.1%)
	Gastritis	0	2 (1.1%)
	Gastro-intestinal disorders	1 (0.5%)	4 (2.2%)
	Heartburn	1 (0.5%)	2 (1.1%)
	Nausea	5 (2.6%)	5 (2.7%)
	Others[a,b]	3 (1.6%)	6 (3.2%)
Body as a whole general	Headache	2 (1.1%)	1 (0.5%)
	Tiredness	1 (0.5%)	2 (1.1%)
	Others[a,b]	9 (4.7%)	2 (1.1%)
Total number	Subjects	24 (12.6%)	30 (16.3%)
Total number	Events	34	43

a The following were reported in 1 patient each in the aceclofenac group: exanthema, folliculitis, joint pain, localized numbness,upper abdominal pain, abdominal cramp, abnormal hunger, abnormal liver function tests, extrasystoles, thrombopenia, general pain, weight increase.

b The following were reported in 1 patient each in the naproxen group: intraocular pressure increased, dyspepsia, epigastric food related pain, eructation, abdominal fullness, tender liver, vomiting, allergy.

Eleven of the adverse events, possibly related to the treatment, reported by 5 patients in the aceclofenac group and 9 adverse events reported by 6 patients in the naproxen group were associated with withdrawal from the study. The adverse events reported in the aceclofenac group were abdominal pain (2), diarrhoea (1), itching (1), exanthema (1), nausea (1), lethargy (1), painful joint (1), weight gain (1), thrombopenia (1) and abnormal liver function test results (1). In the naproxen-group they were nausea (3), constipation (1), itching (1), epigastric non-food related pain (1), bloating (1), vomiting (1) and headache (1).

A non-significant increase in liver function values was noted in several patients of both groups. Since many of these patients had elevated values at the beginning of the trial or were receiving concurrent medication, no clear connection to the study medication could be established.

DISCUSSION

In the absence of drugs which exert a beneficial protective effect on cartilage breakdown, the therapy of osteoarthritis is generally directed towards management of joint pain and any associated inflammation (14). In this respect, NSAIDs represent an important part of the drug armamentarium. The results of this randomized, double-blind study in patients with osteoarthritis indicate that the new NSAID aceclofenac given for 12 weeks is as effective as naproxen in relieving pain. No statistically significant differences were found between the two treatment groups. In both groups, clear improvement compared to pretreatment values was noted for all of the clinical parameters used to characterize this disease. In both groups of patients there was, for example, a reduction in the pain on pressure, on movement and at rest in more than three-quarters of the treated patients as well as a decrease in joint swelling and an increase in functional capacity of the affected joint. At the same time, the duration of joint stiffness was decreased. This symptomatic improvement cannot just be attributed to a placebo effect, since even with a shorter treatment period of 4 weeks, aceclofenac has been shown to produce significantly greater improvement than placebo in pain intensity, joint swelling and tenderness in patients with osteoarthritis of the knee, using the same inclusion criteria as those in the present study (11). The relatively high number of patients in each treatment group who withdrew because of complete relief of symptoms may have been related to the fact that 13 subjects were included in the intention-to-treat analysis who did not fulfill the criteria of active disease. The good efficacy of aceclofenac was confirmed by the overall evaluation of the status of the disease. In 75% of the cases in the aceclofenac group, the investigators noted an improvement over baseline conditions. For the naproxen group the comparative percentage was 68.8%.

In osteoarthritis, aceclofenac has been shown to be as effective as diclofenac in the management of joint pain (9,10,12). Of particular interest in these previous studies was the significantly better tolerability of aceclofenac in comparison to diclofenac. In healthy volunteers, aceclofenac also tended to cause less gastrointestinal blood loss than diclofenac (16).

In the present study, in general, tolerability of both drugs was good. The total number of adverse events in the aceclofenac group was significantly fewer than in the reference group of naproxen patients. Altogether, adverse drug reactions were reported by 24 patients or 12.6% of the aceclofenac group. In 19 of these 24 patients, the side-effects involved the gastrointestinal tract, whereas the comparative figure for the naproxen group was higher at 36 patients.

Gastrointestinal disturbances are the main adverse effects of NSAIDs in the long-term therapy of osteoarthritis and are a major factor in the determination of the most suitable drug (17). The improved tolerability of aceclofenac in comparison to naproxen suggests that the former represents a good alternative to some other NSAIDs. An additional factor in favour of aceclofenac is that it has been shown to inhibit interleukin 1β (IL 1β) production by mononuclear cells in osteoarthritis (13). IL 1β is one of the cytokines thought to be involved in the process of cartilage breakdown in osteoarthritis (18) and its inhibition could contribute towards the clinical efficacy of aceclofenac. In conclusion, based on the knowledge available to date, aceclofenac can be considered as an alternative NSAID for osteoarthritis with good efficacy and tolerability.

Acknowledgements: We thank all physicians who participated in this study for their co-operation and Dr. J. Maisenbacher and Dr. M.J. Parnham for assistance with the manuscript. The investigation was sponsored by Prodesfarma S.A., Sant Just Desvern, Barcelona, Spain.

REFERENCES

1. Grau M, Guasch J, Montero JL, Felipe A, Carrasco E, Julià S. Pharmacology of the potent new nonsteroidal anti-inflammatory agent aceclofenac. Arzneim-Forsch/Drug Res 1991, 41, 1265-1276.
2. Cecchetin M, Cerea P, Torri G. Therapeutic efficacy of aceclofenac and diclofenac in acute knee arthroses. Study of the E_2-Prostaglandin levels in the synovial fluid and in the serum. Clin Trials J, 1988; 25: 144-151.
3. Torrejón VA. Treatment of severe rheumatic pain with aceclofenac. Results of a comparative study vs placebo. Acta Ther, 1988; 14: 275-280.
4. Ballesteros R, Ansoleaga JJ, Tapounet R. The efficacy and tolerance of aceclofenac in rheumatoid arthritis. A double-blind study vs placebo. Clin Trials J, 1990; 27: 12-19.
5. 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: 175183.
6. Dawson AJ, Roma J, Bowdler JM. Aceclofenac in the treatment of rheumatoid arthritis: a multicentre, double-blind, randomised placebo-controlled study. Eur J Rheumatol Inflam. In press.
7. Martín-Mola E, Gijón-Baños J, Ansoleaga JJ. Aceclofenac in comparison to ketoprofen in the treatment of rheumatoid arthritis. Rheumatol Int. In press.
8. Hunter JA, Parnham MJ, Gras X. Aceclofenac in rheumatoid arthritis: a useful and novel anti-inflammatory. Clin rheumatol. In press.

9. Dias C, Rodriguez A, Geli C, Llobet JM, Tapounet R. Comparison of aceclofenac and diclofenac in osteoarthritic pain. Curr Ther Res, 1988; 44: 252-256.
10. Grupo de Estudio de Gonartrosis. Eficacia y tolerancia de aceclofenac en el tratamiento de la gonartrosis. Rev Esp Reumatol, 1992; 19: 142-146.
11. Birrell DH, Roma J, Bowdler JM. Evaluation of the efficacy and safety of aceclofenac in the treatment of osteoarthritis. Br J Clin Res 1995; 6: 45-55.
12. Ward DE, Veys EM, Bowdler JM, Roma J. Comparison of aceclofenac with diclofenac in the treatment of osteoarthritis. Clin Rheumatol. In press.
13. González E, De la Cruz C, Nicolás R, Egido J, Herrero-Beaumont, G. Longterm effect of non-steroidal antiinflammatory drugs on the production of cytokines and other inflammatory mediators by blood cells of patients with osteoarthritis. Agents and Actions, 1994; 41: 171-178.
14. Al Arfag A, Davis P. Osteoarthritis 1991. Current drug treatment regimens. Drugs, 1991; 41: 193-201.
15. Dromgoole SH, Furst DE. Naproxen. Paulus HE, Furst DE, Dromgoole SH, Editors. Drugs for rheumatic diseases. New York, Edinburgh, London, Churchill Livingstone, 1987, 347-364.
16. Wassif W, Bjarnason I. A comparison on the effects of aceclofenac and diclofenac on gastrointestinal blood loss. Br J Clin Res, 1992; 3: 109-114.
17. Brandt KD. Osteoarthritis: treatment guidelines. Drug Therapy, 1988; 18: 26-40.
18. Hamerman D. The biology of osteoarthritis. New Engl J Med, 1989; 320: 1322-1330.

Received: 18 December 1995.
Revision-accepted: 30 May 1996.
Correspondence to: Dr. E. MONTULL,
Prodesfarma Research Centre, P.O. Box 26, E-08960 Saint Just Desvern (Barcelona), SPAIN.