Expert Opinion

Aceclofenac in the management of inflammatory pain

Erik Legrand
Service Rheumatologie, CHU Angers, 4 rue Larrey 49933, Angers Cedex 9, France

Aceclofenac (Almirall Prodesfarma SA) is an oral NSAID that is effective in the treatment of painful inflammatory diseases and has been used to treat > 75 million patients worldwide. It has proved as effective as diclofenac, naproxen and piroxicam in patients with osteoarthritis, diclofenac, ketorolac, tenoxicam and indomethacin in patients with rheumatoid arthritis and tenoxicam, naproxen and indomethacin in patients with ankylosing spondylitis. It also provides effective analgesia in other indications, such as dental or gynaecological pain, lower back pain and ear, nose and throat indications. Aceclofenac appears to be particularly well-tolerated amongst the NSAIDs, with a lower incidence of gastrointestinal adverse effects. This good tolerability profile results in a reduced withdrawal rate and hence greater compliance with treatment.

Keywords: aceclofenac, arthritis, gastrointestinal, NSAIDs, pain

Expert Opin. Pharmacother. (2004) 5(6):1347-1357

1. Overview of the market

Osteoarthritis, rheumatoid arthritis (RA) and ankylosing spondylitis are a group of related, but distinct, disorders of the cartilage of osteoarticular joints.

Osteoarthritis is a degenerative, progressive disorder that predominantly affects the large weight-bearing joints, although other joints can be involved. The clinical characteristics include morning stiffness of short duration, stiffness or 'gelling' on rest, pain on use, joint inflammation and bone deformity. Radiographical changes in the joints may include irregular narrowing of the joint space, subchondral sclerosis and cyst and osteophyte formation. Osteoarthritis is extremely common in the elderly, with an prevalence of 85% in the 75- to 90-year-old population and many patients consider it to be a normal part of the ageing process. Unfortunately, the reduction in mobility caused by osteoarthritis can lead to social isolation, as well as secondary morbidity. In western societies, population changes in age-profile and obesity predict an increasing incidence of osteoarthritis.

RA is less common than osteoarthritis, although no less debilitating. Although RA shares a number of characteristics with osteoarthritis, it is a systemic, rather than a local disease. Swelling and stiffness typically affect the joints of the neck, shoulders, elbows, wrists and especially the proximal joints of the hands. Hips, knees, ankles and toes can also be affected. Unlike osteoarthritis, joints tend to be affected symmetrically and morning stiffness tends to be of longer duration in RA than in osteoarthritis. Systemic symptoms are also common in RA and include fatigue, malaise, subcutaneous nodules (in ~ 20% of patients) and fever.

Ankylosing spondylitis is characterised by inflammation, predominantly of the spine, but in some cases, also of the large peripheral joints. Systemic symptoms can include fever, fatigue and anorexia and in some cases pericarditis and pleuritis may occur.

Taken together, these various forms of rheumatic disorder are responsible for a prodigious burden of morbidity. It is estimated that there are ~ 100 million people suffering from arthritis or other rheumatic disorders across Europe, ~ 14% of the

 ISSN 1465-6566

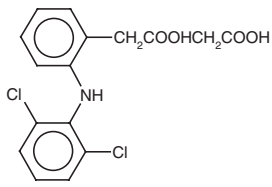

Figure 1. The chemical structure of aceclofenac.

population [1]. Approximately 50% of these are below the age of retirement, although many retire early due to disability or illness.

Since the introduction of acetylsalicylic acid in the nineteenth century, NSAIDs have become widely used in the treatment of these illnesses for their pain-relieving and anti-inflammatory properties. Given the large and growing numbers of patients affected, NSAID use, both prescription and over-the-counter, is now very common. Although the efficacy of new drugs is well-established, their widespread use has prompted concerns over safety, particularly gastrointestinal (GI), safety and the development and introduction of new NSAIDs has attempted to avoid these problems. The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase, a key enzyme in the inflammation cascade. Cyclooxygenase exists as two isoenzymes:

- COX-1: a constitutive enzyme responsible for the formation of prostacyclin and protective and repair functions in the gastric mucosa.
- COX-2: an inducible enzyme responsible for the generation of inflammatory mediators in response to inflammatory stimuli.

The two isoforms of the enzyme have quite different biological properties and functions. Inhibition of COX-1 is responsible for the potentially serious adverse effects of the NSAIDs.

NSAIDs have varying degrees of specificity for the two isoforms of cyclooxygenase but in recent years there has been a concerted effort to develop COX-2 specific agents in an attempt to avoid the GI tolerability problems that can be manifest during long-term use of NSAIDs.

2. Chemistry

Aceclofenac is a phenylacetic acid derivative NSAID with a chemical designation of [2-[(2,6-dichlorophenyl)amino]-phenylacetoxyacetic acid]. The chemical structure is shown in Figure 1.

3. Pharmacodynamics

In vitro studies have shown that aceclofenac inhibits mediators of inflammatory activity, including prostaglandin (PG) E_2, IL-1β, IL-6 and TNF [2]. Interference with the expression of cell adhesion molecules has also been observed in human neutrophils [3].

Aceclofenac has also shown stimulatory effects on glycosaminoglycan synthesis in human osteoarthritic cartilage [4] and chrondroprotective effects mediated by the suppression of metalloprotease production and proteoglycan release in rabbit articular chrondrocytes and human rheumatoid synovial cells [5,6].

Studies using human whole blood assays have shown that aceclofenac and its metabolite 4'-hydroxyaceclofenac inhibit COX-2 (IC_{50} = 0.77 and 36 µM, respectively) but have relatively little effect on COX-1 (IC_{50} = > 100 µM) [7]. These IC_{50} values represent the concentration required to cause a 50% inhibition of COX; the higher the IC_{50} value, the less the inhibitory effect of the compound. Diclofenac, another metabolite of aceclofenac, inhibits both COX-1 and COX-2 (IC_{50} = 0.6 and 0.04 µM, respectively). *In vivo* COX-2:COX-1 selectivity has also been demonstrated for aceclofenac, but not for some other NSAIDs, such as piroxicam, indomethacin, tenoxicam or ketoprofen [8].

In *in vivo* studies in rodents, aceclofenac alleviated pain and fever and had a lower ulcerogenic potential than naproxen or indomethacin and a similar or lower ulcerogenic potential than diclofenac [9,10].

4. Pharmacokinetics and metabolism

Aceclofenac is rapidly and completely absorbed following oral administration [2]. Peak plasma concentrations are achieved relatively rapidly (1.25 – 2 h) and the volume of distribution is ~ 25 l. There is no accumulation with regular dosing, with similar maximum plasma concentrations (C_{max}) and time to C_{max} after single and multiple doses. Aceclofenac is highly bound to plasma proteins (> 99%).

The C_{max}, absorption half-life and volume of distribution of aceclofenac is not affected by age and therefore dose reductions are generally not necessary in elderly patients [11]. Dosage reductions are recommended in patients with hepatic impairment. The presence of food reduces the rate, but not the extent, of absorption of aceclofenac [12].

Aceclofenac is metabolised mainly to 4'-hydroxyaceclofenac, as well as a number of minor metabolites including diclofenac, 5-hydroxyaceclofenac, 5-hydroxydiclofenac and 4'-hydroxydiclofenac [13]. The main route of elimination is via the urine (70 – 80%), mainly as the glucuronides of aceclofenac and its metabolites. The elimination half-life is ~ 4 h.

No important drug interactions have been identified with aceclofenac; those that have been observed are similar to those seen with other NSAIDs. These include interactions with anticoagulants, cyclosporin, diuretics, quinolone antibiotics, lithium, digoxin and methotrexate.

5. Clinical efficacy

5.1 Osteoarthritis

Osteoarthritis is a progressive degenerative condition characterised by joint pain, tenderness, inflammation and restriction

Table 1. Double-blind, controlled studies assessing the efficacy of aceclofenac in patients with osteoarthritis.

N; type of osteoarthritis	Treatment	Duration	Rating instruments	Results	Ref.
397; knee	AC 100 mg b.i.d. DI 50 mg t.i.d.	12 weeks	Investigator assessment of joint pain at rest Joint tenderness, joint effusion, erythema, pain on movement Stiffness, night pain, pain intensity at rest, weight-bearing pain by patient	Similar significant improvement in both groups in investigators' assessments. Patients' assessments: pain relief significantly better with AC	[17]
59; knee and hip	AC 100 mg b.i.d. DI 50 mg t.i.d.	28 days	Pain VAS (Huskisson's)	Similar significant improvement in pain severity in both groups	[18]
335; knee	AC 100 mg b.i.d. DI 50 mg t.i.d.	6 months	LOSI Knee function (extension and flexion)	Similar significant improvements in LOSI and pain in both groups	[19]
240; knee	AC 100 mg b.i.d. PI 20 mg/day	2 months	LOSI Knee function (subjective score) Knee function (goniometer) Pain VAS	Similar significant improvements in both groups on the LOSI and pain	[20]
205; knee	AC 100 mg b.i.d. PI 20 mg/day	3 months	Pain VAS SIG Functional capacity (flexion or extension of knee)	Similar significant improvements in pain, severity and knee extension and flexion in both groups	[21]
374; knee	AC 100 mg b.i.d. NA 500 mg b.i.d.	12 weeks	Investigator assessment of pain Knee flexion (goniometer) Patient assessment of pain intensity, nocturnal pain, pain at rest	Similar significant improvements in pain, joint swelling, joint stiffness and knee function in both groups	[22]

AC: Aceclofenac; DI: Diclofenac; LOSI: Lequense Osteoarthritis Severity Index; N: Number of patients; NA: Naproxen; PI: Piroxicam; SIG: Severity index of gonarthritis; VAS: Visual analogue scale.

in movement. It occurs most commonly in the elderly and the condition is almost universal in those > 80 years of age [14,15]. Amongst Europeans > 65 years of age, it is estimated that at least 50% have radiological signs and 12.5% have a clinical diagnosis of osteoarthritis [16].

Aceclofenac has been proved to be at least as effective as other NSAIDs, including diclofenac, piroxicam and naproxen, in reducing the pain and severity of symptoms and improving functional capacity in patients with osteoarthritis (Table 1) [17-22].

Two large double-blind studies have compared aceclofenac with diclofenac, both of which were carried out in patients with osteoarthritis of the knee. In the first study (n = 397), there was a significant ($p = 0.0001$) improvement in pain intensity from baseline in both groups after 12 weeks, as assessed by the investigator on a five-point pain score scale, with 75 and 70% in the aceclofenac and the diclofenac group, respectively, showing improvement [17]. The other investigator assessments, including joint tenderness, swelling, pain on movement, functional capacity and overall assessment, also revealed a similar significant improvement with both treatments. However, there was a trend towards greater improvement in complete knee movement and reduced pain on movement with aceclofenac and patients with initial flexion deformity experienced a significantly greater improvement in knee flexion with aceclofenac than with diclofenac. The patients' subjective assessment of pain relief also revealed a significant advantage for aceclofenac, with 71% of patients reporting an improvement in pain intensity compared with 59% in the diclofenac group ($p = 0.005$) [18]. In the second study (n = 335), both treatments resulted in a similar significant improvement in the Lequesne Osteoarthritis Severity Index (LOSI) and pain evaluated on a Visual Analogue Scale (VAS) after 15 days versus baseline ($p < 0.001$) [19,18]. From 100% baseline values, the OSI was reduced at the end of the study to 55 and 57% with aceclofenac and diclofenac, respectively, and the pain VAS score to 54% in both groups. Significant improvements were also observed in knee function and knee flexion; these effects were maintained over the 6-month study.

Aceclofenac has also been compared with piroxicam in two large double-blind studies in patients with osteoarthritis of the knee. In a 2-month study, similar significant improvements versus baseline in pain intensity and functional capacity of the knee, as assessed by the OSI, were seen with aceclofenac and piroxicam in 240 patients ($p < 0.001$) [20]. This was supported by significant improvement in the patients' assessment of pain intensity using a VAS ($p < 0.001$) and the investigators' assessments of knee function, extension and flexion ($p < 0.01$). However, the improvement in knee flexion was more rapid with aceclofenac than with piroxicam, with significant effects occurring after 2 weeks of aceclofenac treatment, but only after 1 month of piroxicam treatment. Similar results were reported in the other study (n = 205), with significant

Table 2. Double-blind, controlled studies assessing the efficacy of aceclofenac in patients with rheumatoid arthritis.

N	Treatment	Duration	Rating instrument	Results	Ref.
169	AC 100 mg b.i.d. KE 50 mg t.i.d.	3 months	Pain VAS RI Grip strength Subjective assessment of morning pain Duration of morning stiffness Functional capacity according to Steinbrokers criteria	Similar significant improvements in RI, pain, grip strength, morning stiffness and pain, pain on movement, nocturnal pain and functional capacity	[24]
55	AC 100 mg b.i.d. KE 50 mg t.i.d.	6 months	RI Spontaneous morning pain, pain on movement, nocturnal pain (unspecified) Duration of morning stiffness Handgrip strength Functional capacity (unspecified)	AC faster acting than KE, AC more effective than KE in improving pain at rest, pain on movement and RI	[25]
343	AC 100 mg b.i.d. DI 50 mg t.i.d.	6 months	Pain VAS RI Duration of morning stiffness Grip strength	Similar significant improvements in pain, RI, handgrip and morning stiffness	[26]
219	AC 100 mg b.i.d. IN 50 mg b.i.d.	12 weeks	Number of painful and swollen joints Duration of morning stiffness Grip strength ARA functional class Investigator and patient global assessment	Similar significant improvements in the number of painful and swollen joints, grip strength, duration of morning stiffness, pain intensity and functional class in both groups	[22]
237	AC 100 mg b.i.d. TX 20 mg/day	3 months	RI Grip strength Number of patients with morning stiffness Pain VAS	Similar significant improvements in RI, grip strength, morning stiffness and pain intensity in both groups	[28]

AC: Aceclofenac; ARA: American Rheumatism Association; DI: Diclofenac; IN: Indomethacin; KE: Ketoprofen; LOSI: Lequense Osteoarthritis Severity Index; N: Number of patients; RI: Ritchie index; SIG: Severity index of gonarthritis; TX: Tenoxicam; VAS: Visual analogue scale.

improvements in pain (VAS), severity index for gonarthritis and knee flexion and extension in both groups ($p < 0.01$) [21].

Finally, aceclofenac proved as effective as naproxen in 374 patients, again with osteoarthritis of the knee [22]. Both treatments resulted in significant improvements in pain at rest, pain on movement and pain from pressure on the joint ($p < 0.05$), with an improvement in overall pain being reported in 76 – 86% of patients. This was accompanied by a reduction in joint swelling and stiffness and an improvement in knee function. Functional capacity was improved in 81 and 84% of aceclofenac- and naproxen-treated patients, respectively. An overall improvement of the condition was seen as early as week 2 in 56% of patients treated with aceclofenac and 48% treated with naproxen. At the end of the study, the investigators reported an overall improvement in 73 and 69% of patients in the aceclofenac and the naproxen group, respectively.

5.2 Rheumatoid arthritis

RA is a chronic condition characterised by inflammation of the peripheral joints of the feet, hands, wrists, ankles and elbows. It affects ~ 1% of the population in Europe, is two to three times more common in women than in men and tends to first manifest itself at ~ 30 years of age [23].

Double-blind studies have confirmed that the efficacy of aceclofenac in patients with RA is at least comparable to that of ketoprofen, indomethacin, diclofenac and tenoxicam (Table 2) [24-28].

A relatively small, double-blind study indicated that aceclofenac was more effective and faster acting than ketoprofen in patients with RA [24,25]. However, a subsequent larger study failed to prove any clear superiority of aceclofenac over ketoprofen, although the improvement was again more rapid, with a significant reduction in the Ritchie Index (RI) (evaluation of joint tenderness) occurring after 15 days ($p < 0.001$) with aceclofenac, but not until 1 month with ketoprofen ($p < 0.05$) [19,25]. All other parameters, including pain (VAS), grip strength, morning stiffness and pain, pain on movement, nocturnal pain and functional capacity, were improved similarly with both treatments. A total of 4 patients in the aceclofenac group and 11 in the ketoprofen group, withdrew from the study prematurely due to inefficacy. Similar differences in favour of aceclofenac compared with other NSAIDs have been reported in terms of withdrawal due to adverse events and hence overall acceptability (see Section 6) [19,29].

A double-blind study in 343 patients showed that aceclofenac and diclofenac were equally effective in improving pain (VAS), morning stiffness, RI and handgrip [26]. The overall assessment of efficacy by the patient and investigator at the end of the study was good to very good in 70 and 76% of cases, treated with aceclofenac and 66 and 70% of cases

Table 3. Double-blind, controlled studies assessing the efficacy of aceclofenac in patients with rheumatoid arthritis.

N	Treatment	Duration (months)	Rating instruments	Results	Ref.
273	AC 100 mg b.i.d. TX 20 mg/day	3	Duration of morning stiffness Pain VAS Objective mobility assessment indices	Similar significant improvements in morning stiffness, pain, modified Schöber's test, C7-iliac crest distance, lateral flexion of the spine, thoracic expansion and occiput-wall distance	[30]
126	AC 100 mg b.i.d. NA 500 mg b.i.d.	3	Pain VAS Pain on movement Pain at rest Chest expansion Hand-to-floor distance Schöber's test Capacity to perform normal daily activities	Similar significant improvement in spontaneous pain, pain on movement and at rest, chest expansion, hand-to-floor distance, Schöber's test and normal daily activities	[31,32]
310	AC 100 mg b.i.d. IN 25 mg b.i.d. and 50 mg/day	3	Pain VAS Morning stiffness Modified Schöber's test C7-iliac crest line measurement Patient global assessment	Similar significant improvements in pain, morning stiffness, modified Schöber's test, C7-iliac crest distance and lateral spine flexion	[32]

AC: Aceclofenac; IN: Indomethacin; N: Number of patients; NA: Naproxen; TX: Tenoxicam; VAS: Visual analogue scale.

treated with diclofenac, respectively. Similarly, in a comparison with indomethacin in 219 patients, the improvements in the number of painful and swollen joints, grip strength, duration of morning stiffness, pain intensity and American Rheumatism Association (ARA) functional class were comparable with both treatments [22,27].

5.3 Ankylosing spondylitis

Ankylosing spondylitis is characterised by inflammation of the spine and large peripheral joints. Patients suffer from cyclical back pain and morning stiffness, as well as systemic symptoms such as fever, fatigue, weight loss and anaemia. The prevalence in Europe is estimated to be 0.2 – 1%, and the condition is more common in men than in women and amongst those with a family history of the disorder.

Aceclofenac has been proved to be as effective as naproxen, tenoxicam and indomethacin in double-blind studies carried out in patients with ankylosing spondylitis (Table 3) [30-32].

When compared with tenoxicam in a 3-month, double-blind study in 273 patients, aceclofenac was as effective in improving morning stiffness, pain (VAS), the modified Schöber's test, the C7-iliac crest distance, lateral flexion of the spine, thoracic expansion and the occiput-wall distance [30]. Aceclofenac tended to be superior, with regard to occiput-wall distance, whilst there was a trend in favour of tenoxicam in lateral spinal flexion and thoracic expansion. Both drugs were rated as 'good' at the end of the study, with morning stiffness improving by 68 and 65% in the aceclofenac and tenoxicam groups, respectively, and the pain VAS score improving by 45% in both groups. There were no significant differences between the groups regarding the need for additional paracetamol.

In another 3-month, double-blind study that enrolled 126 patients, aceclofenac and naproxen both resulted in similar improvements in spontaneous pain (VAS), pain on movement, pain at rest, chest expansion, hand-to-floor distance and the Schöber's test [31]. Most patients in both groups also improved their capacity to perform normal daily activities, with no significant differences between the two treatments. At the end of the study, the overall efficacy assessment by the physician and the patients was similar for the two groups.

Aceclofenac was also compared with indomethacin in a 3-month study that enrolled 310 patients [32]. Pain (VAS), morning stiffness, modified Schöber's test, C7-iliac crest distance and lateral spine flexion all improved significantly with both drugs, with no significant differences between the groups. The pain VAS score and morning stiffness improved by 37 and 51%, with aceclofenac and 41 and 46%, with indomethacin, respectively. Other variables including chest expansion, occiput-wall distance, Likert pain score, use of paracetamol rescue and the patient and physician global assessment also showed similar significant improvements from baseline.

5.4 Analgesic effects

A small, double-blind study (n = 12) compared the effects of aceclofenac and diclofenac on PGE_2 levels in the synovial fluid of patients suffering from acute knee pain with synovial effusion [33]. Both aceclofenac 75 mg t.i.d. and diclofenac 50 mg t.i.d. resulted in a progressive marked reduction in joint pain and an improvement in joint function during the 6-day study, although the effect was somewhat more rapid with aceclofenac. Only aceclofenac resulted in a significant reduction in synovial fluid levels of PGE_2 from baseline (113.0 – 66.8 pg/ml).

It is estimated that ~ 80% of the European population will experience back pain lasting for at least 1 day at some time during their lives [34]. In many of these, the problem with recur

and will be associated with considerable morbidity. Aceclofenac (150 mg b.i.d. i.m. for 2 days + 100 mg b.i.d. p.o. for 5 days) was also more effective than diclofenac (75 mg b.i.d. i.m. for days + 50 mg t.i.d. p.o. for 5 days) in 100 patients with acute lumbago, as assessed by the physicians' overall assessment of efficacy, alleviation of functional impairment and pain (VAS) [35]. The physician's assessment of efficacy was at least good in 85% of aceclofenac-treated patients, compared with 76% of those given diclofenac ($p < 0.05$). In a larger, double-blind study, in 227 patients with acute lower back pain, aceclofenac 100 mg b.i.d. and diclofenac 75 mg b.i.d. resulted in a similar significant improvement in pain at rest (VAS), with a trend towards a greater improvement with aceclofenac [36]. After 8 – 10 days, the mean change in pain score at rest compared with baseline was 61.6 mm with aceclofenac and 57.3 mm with diclofenac. The change in the mean pain score on movement versus baseline was also greater with aceclofenac (61.4 mm) than with diclofenac (56.7 mm). Improvements in functional impairment and ability to perform routine daily activities were also greater in the aceclofenac group. A total of six patients in the aceclofenac group, but only one in the diclofenac group, withdrew prematurely due to early cure.

In two comparative studies, involving a total of 99 patients, aceclofenac 100 mg was shown to be more effective than paracetamol 650 mg in the relief of postepisiotomy pain [37,38]. Single doses of aceclofenac 100 or 150 mg have been shown to provide effective analgesia in patients with moderate-to-severe dental pain and those undergoing third molar extraction [39-41]. Other indications in which aceclofenac has proved effective include dysmenorrhoea and musculoskeletal trauma such as contusions and sprains [42-44].

6. Safety and tolerability

6.1 General safety

Apart from those associated with the GI system, the most common adverse events seen with aceclofenac are dizziness, vertigo, pruritus, rash and dermatitis. However, these events occur in only a small proportion of patients and the overall tolerability profile of aceclofenac has been shown to be similar to that of placebo in patients with rheumatic disorders [45]. Elevated liver enzymes occur in ~ 2.5% of patients, which is a similar incidence to that observed with other NSAIDs, such as diclofenac, indomethacin, naproxen, piroxicam and tenoxicam. Other non-GI adverse effects are very rare, typically occurring with frequencies of < 1%.

A large, 12-month, prospective, community-based study complying with the Safety Assessment of Marketed Medicines (SAMM) guidelines has been carried out in patients with osteoarthritis, RA or ankylosing spondylitis [29]. A total of 10,142 patients were enrolled, 7890 of whom were treated with aceclofenac 100 mg b.i.d., and 2252 with diclofenac 75 mg b.i.d. The overall incidence of adverse events was significantly lower with aceclofenac than with diclofenac ($p < 0.001$), as was the percentage of patients discontinuing the study due to adverse events ($p < 0.001$) (Figure 2). There were no reports of any serious hepatic adverse events in either group.

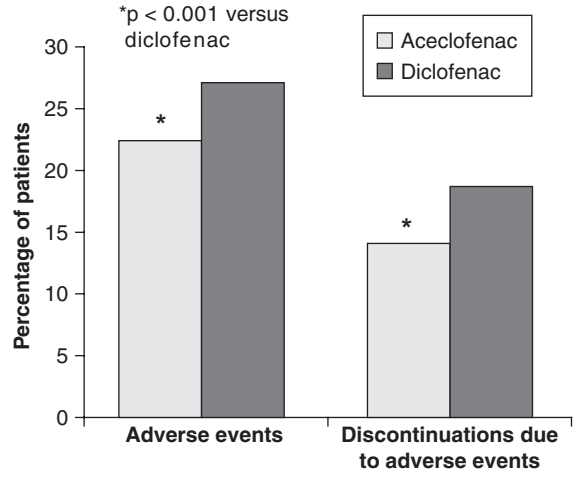

Figure 2. Individual incidence of overall adverse events and discontinuations due to adverse events with aceclofenac and diclofenac in patients enrolled in the SAMM study [29].
SAMM: Safety Assessment of Marketed Medicines.

In double-blind, controlled studies, the overall incidence of adverse events was significantly lower with aceclofenac than with naproxen (45 versus 55 events; $p = 0.025$) in 374 patients with osteoarthritis [22], and than with indomethacin (42 versus 75 events; $p = 0.006$) in 219 patients with RA [27]. In another comparison with naproxen, the overall tolerability of aceclofenac was rated as significantly better by physicians and patients ($p < 0.05$) [32]. In another comparison with indomethacin, there was no difference in the overall incidence of adverse events, although CNS symptoms (mainly headache and dizziness) were significantly less common with aceclofenac (2.6 versus 13.7%; $p < 0.001$) [32]. The percentage of patients discontinuing treatment due to adverse events was also significantly lower with aceclofenac than with ketoprofen (2.3 versus 13.4%; $p < 0.01$) in 169 patients with RA [24] and than with diclofenac (8.2 versus 16.4%; $p < 0.05$) in 335 patients with osteoarthritis [19].

In a meta-analysis of 13 double-blind, randomised studies involving 3574 patients with osteoarthritis, RA or ankylosing spondylitis, those receiving aceclofenac were 1.38 times (95% CI = 1.19 – 1.60; $p < 0.001$) more likely to be free of adverse events than those taking other NSAIDs (diclofenac, indomethacin, naproxen, piroxicam, tenoxicam or ketoprofen) [46]. In addition, the number of withdrawals due to adverse events was also significantly lower with aceclofenac than with the comparator NSAIDs (odds ratio 0.67; 95% CI = 0.52 – 0.86; $p = 0.002$).

In terms of hepatic safety, aceclofenac may elevate circulating levels of hepatic enzymes; the incidence of such elevations is similar to that seen with diclofenac, indomethacin, naproxen, piroxicam and tenoxicam [2].

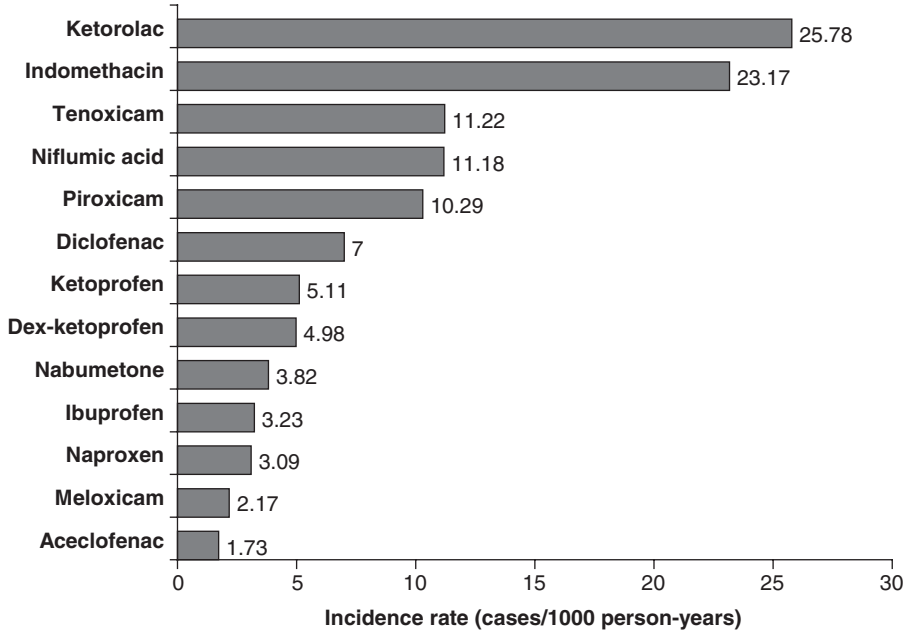

Figure 3. Incidence rate (cases per 1000 person-years) of upper gastrointestinal bleeding with NSAIDs [49].

7. Gastrointestinal safety and tolerability

GI adverse events, such as nausea, diarrhoea, flatulence, constipation, vomiting, bleeding and ulcers, are the most common tolerability problems with all NSAIDs. However, evidence indicates that aceclofenac has a particularly good GI tolerability profile.

In the previously discussed SAMM study [29], the most common adverse events in both groups were GI-associated. However, the overall incidence of GI adverse events was significantly lower with aceclofenac than with diclofenac (10.6 versus 15.2%; $p < 0.001$), as was the incidence of the four most common adverse events: dyspepsia (5.4 versus 6.7%; $p = 0.017$), abdominal pain (2.5 versus 4.4%; $p < 0.001$), diarrhoea (1.5 versus 3.6%; $p < 0.001$) and nausea (1.6 versus 2.4%; $p = 0.01$). In addition, the incidence of nausea, abdominal pain and diarrhoea leading to discontinuation was, respectively, 46, 65 and 41 lower with aceclofenac than with diclofenac ($p < 0.001$).

The effect of aceclofenac and diclofenac on the gastroduodenal mucosa has been specifically studied endoscopically in a double-blind, placebo-controlled study in 30 healthy volunteers [47]. Endoscopic findings were graded according to the modified Lanza score. Following administration of placebo, aceclofenac 150 mg/day or sodium diclofenac 75 mg/day for 2 weeks, there was significantly more gastropathy in the diclofenac group than in the aceclofenac and placebo groups ($p < 0.05$). No significant differences were observed between the aceclofenac and placebo groups. Gastric mucosal content of hexosamine, a factor that is known to have a protective effect on cells and gastroduodenal blood flow were also significantly reduced by diclofenac. It has been suggested that impairment of mucosal microcirculation might play an important role in NSAID gastropathy. In contrast, aceclofenac significantly increased hexosamine content and had no effect on blood flow. Similarly, in a 10-day double-blind study in 12 healthy volunteers, diclofenac 50 mg t.i.d. resulted in a significant increase in GI blood loss (0.59 ml) whilst the increase with aceclofenac (0.29 ml) was not significant [48].

Superior GI tolerability of aceclofenac compared with diclofenac has also been reported in double-blind, controlled trials in patients with rheumatic disorders [17,19,26-36]. Similar advantages for aceclofenac in terms of GI adverse events are seen in double-blind studies with other NSAIDs. For example, in a comparison of aceclofenac and piroxicam in 205 patients with osteoarthritis, GI intolerance was reported by twice as many piroxicam-treated as aceclofenac-treated patients (14 versus 7) [21,22]. In another comparison with piroxicam (n = 240), there were twice as many reports of faecal blood loss in the piroxicam group than in the aceclofenac group [20]. A significantly higher incidence of withdrawals due to GI adverse events was reported with ketoprofen than with aceclofenac (9 versus 1; $p < 0.01$) in 169 patients with RA [24]. In the meta-analysis of 13 studies discussed in the previous section [46,48], patients taking aceclofenac were 1.52 times more likely to be free of GI adverse effects than those receiving comparator NSAIDs (95% CI = 1.29 – 1.80; $p < 0.001$) and the incidence of withdrawals due to GI effects was 52.5% lower (95% CI = 0.34 – 0.65; $p < 0.001$).

A specific, population-based analysis has recently been carried out to compare the incidence of upper GI bleeding between 13 various NSAIDs [49]. Data were collected over a 4-year period from 180,995 patients in a Spanish health

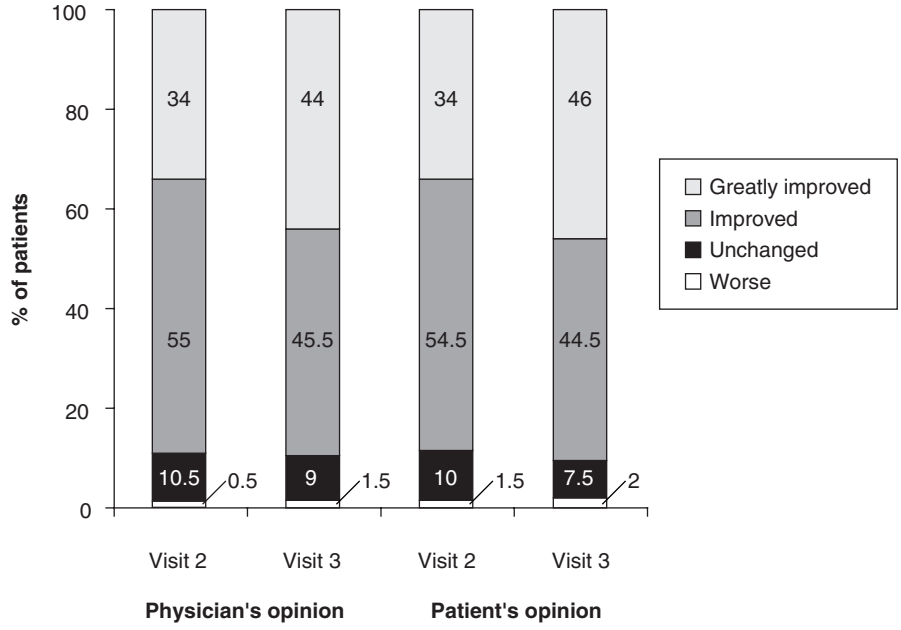

Figure 4. Evaluation of status by the physician and the patient amongst patients suffering from acute post-traumatic pain [50].

authority area. The incidence of upper GI bleeding varied markedly, ranging from 1.7 for aceclofenac to 25.8/1000 person-years for ketorolac (Figure 3). Taking aceclofenac as the reference to assess the relative risk for each NSAID, those with a relative risk of ≥ 4 (i.e., diclofenac, piroxicam, niflumic, tenoxicam, indomethacin and ketorolac) were considered to be statistically worse than aceclofenac. Thus, aceclofenac had the lowest risk of upper GI tract bleeding.

8. Compliance

As many patients with rheumatic disorders will require long-term therapy, it is essential that medications are well-tolerated, as well as effective, in order to ensure good compliance. Therefore, a pan-European observational cohort study has recently been conducted in order to determine whether the good tolerability profile of aceclofenac is associated with good patient acceptability [50]. A total of 23,407 patients who were treated with aceclofenac for pain, due to various inflammatory or degenerative rheumatic diseases, were asked to evaluate their treatment in terms of pain evolution, patient overall status and overall satisfaction with treatment. Physician evaluations were also performed for patient overall status and compliance. The patients considered aceclofenac to be a highly effective treatment, with fast and prolonged analgesic effects. The patient overall status was considered improved or much improved in 84% of cases, > 94% of patients were compliant with treatment and 93.5% expressed overall satisfaction at the final visit (visit 3). These findings were similar irrespective of whether the pain was acute, semichronic or chronic. However, the greatest treatment difference was seen amongst patients suffering from acute disease, such as post-traumatic pain (Figure 4).

These findings support those from the meta-analysis of 13 double-blind, randomised studies involving > 3500 patients with osteoarthritis, RA or ankylosing spondylitis [46]. Patients treated with aceclofenac were significantly more likely to complete the treatment than those treated with diclofenac, indomethacin, naproxen, piroxicam, tenoxicam or ketoprofen (odds ratio 1.37; 95% CI = 1.17 – 1.60; $p < 0.001$). When the data were analysed according to disease, this significant difference remained for osteoarthritis and RA, although not for ankylosing spondylitis. As discussed previously, the number of withdrawals due to adverse events and GI adverse events was significantly lower with aceclofenac than with the comparator NSAIDs.

9. Cost-effectiveness

Although aceclofenac is similar in terms of efficacy to other NSAIDs, its superior tolerability and compliance indicate that there may be economic consequences. A decision analytical model was therefore constructed using data from 12 double-blind randomised trials conducted in patients with osteoarthritis, RA or ankylosing spondylitis [51]. Despite substantial differences in drug acquisition costs (US$0.18 – 0.73/day), there were no significant differences between aceclofenac and the comparator NSAIDs (diclofenac, indomethacin, ketoprofen, naproxen and tenoxicam) in terms of total costs, although piroxicam was significantly less expensive overall and

iatrogenic costs were lower for aceclofenac than for comparators. This was attributable to the considerably lower iatrogenic costs associated with aceclofenac (i.e., costs related to treatment of adverse events and substitution treatment after NSAID discontinuation), even though the cost of acquisition was higher for aceclofenac than for the other NSAIDs. Although there are criticisms of this type of study [52] and some of the results appear anomolous, the study does suggest that the higher cost of aceclofenac is more than compensated for by its reduced iatrogenic effects.

10. Expert opinion

The NSAID market is undoubtedly crowded and competitive, with new compounds being introduced frequently and older drugs being almost as frequently withdrawn or relabelled. In order to prosper, medications in this area in particular need to offer specific and tangible benefits. Diclofenac is the gold-standard medication for inflammatory arthritic conditions, being both effective and inexpensive, although its tolerability lags behind the best of the newer drugs. Although a new drug in some markets, aceclofenac has been used in clinical practice for > 10 years. It is registered in > 60 countries worldwide and around 75 million patients have been treated, and in excess of 1 billion defined daily doses administered. Depending on the country, aceclofenac may be available as tablets, sachets, a cream and an injection.

It is within this context that the place of aceclofenac in therapy needs to be considered, not only in terms of its absolute efficacy, safety, tolerability and compliance, but also when measured against the therapeutic alternatives, particularly diclofenac.

The objective of drug treatment in osteoarthritis, RA and ankylosing spondylitis is to reduce inflammation, ameliorate pain and improve joint function and mobility. On this basis, it is clear from the foregoing analysis that the overall efficacy of aceclofenac is equivalent to that of diclofenac in osteoarthritis and RA, to naproxen in osteoarthritis and ankylosing spondylitis, to indomethacin in RA and ankylosing spondylitis and to piroxicam in osteoarthritis, to ketoprofen and tenoxicam in RA, and tenoxicam in ankylosing spondylitis. This is not unexpected as all of the NSAIDs are potent inhibitors of cyclooxygenase. Although there is a general lack of differential efficacy between all of the NSAIDs, this does not mean that they are all equivalent to each other in terms of efficacy; variations in individual patient responses to NSAIDs require a degree of adaptation of therapy to find the best solution for each patient [53,54]. The differing efficacy and adverse effect profile of the various NSAIDs allow therapy to be better tailored to the individual needs of the patient.

Given their broadly equivalent efficacy, the key issues for NSAIDs are safety and tolerability, particularly their propensity to cause upper GI bleeding. In this respect, aceclofenac appears to have an advantage over the majority of other NSAIDs. A meta-analysis of 13 double-blind, randomised, controlled studies indicated that aceclofenac had the lowest incidence of upper GI bleeding of any of the agents included in the analysis [46]. In comparative studies, even where the rate of GI symptoms was equivalent, there were generally fewer withdrawals due to side effects with aceclofenac than with comparator agents. Endoscopic studies, although their applicability to the clinical situation has been questioned, confirm that aceclofenac causes less gastromucosal damage than diclofenac [47]. The large, community-based study SAMMs showed a statistically significant advantage for aceclofenac compared with a sustained release preparation of diclofenac [29]. A further postmarketing study comprising of > 180,000 patients also showed that aceclofenac had the lowest incidence of upper GI effects of any of the 13 NSAID medications included [49].

Upper GI bleeding, pain and discomfort are the predominant adverse effects of all NSAIDs and, as well as being potentially life-threatening, can frequently lead to interruption or cessation of treatment. The improved safety profile of aceclofenac in this respect contributes not only to better patient acceptability, but better compliance as well. Thus, when compared with other NSAIDs, patients treated with aceclofenac can expect not only fewer GI adverse effects, but to be able to tolerate their medication better and consequently benefit from better control of their symptoms.

Overall, short- and medium-term studies show that aceclofenac is as effective as other NSAIDs and in particular is comparable in this respect with the gold-standard diclofenac. In contrast, the GI tolerability of aceclofenac appears to be not only as good as the best of the alternative NSAIDs but also significantly better than the majority. This has been shown to result in better patient acceptability and hence better compliance [50].

Bibliography

1. JONES R: Manifesto for the Third Millennium. *The Patient's Network* (2000) 5:Number 3.
2. DOOLEY M, SPENCER CM, DUNN CJ: Aceclofenac. A reappraisal of its use in the management of pain and rheumatic disease. *Drugs* (2001) 61:1351-1378.
3. GONZALEZ-ALVARO I, CARMONA L, DIAZ-GONZALEZ F *et al.*: Aceclofenac, a new nonsteroidal antiinflammatory drug, decreases the expression and function of some adhesion molecules on human neutrophils. *J. Rheumatol.* (1996) 23:723-729.
4. DINGLE JT, PARKER M: NSAID stimulation of human cartilage matrix synthesis. *Clin. Drug Invest.* (1997) 14:353-362.
5. AKIMOTO H, YAMAZAKI R, HASHIMOTO S *et al.*: 4'-Hydroxyaceclofenac suppresses the interleukin-1-induced production of promatrix metalloproteinases and release of sulfated-glycosaminoglycans from rabbit articular chondrocytes. *Eur. J. Pharmacol.* (2000) 401:429-436.
6. YAMAZAKI R, KAWAI S, MIZUSHIMA Y *et al.*: A major metabolite of aceclofenac,

4'-hydroxy aceclofenac, suppresses the production of interstitial pro-collagenase/proMMP 1 and pro-stromyelsin-1/proMMP-3 by human rheumatoid synovial cells. *Inflamm. Res.* (2000) 49:133-138.

7. HENROTIN Y, DE LEVAL X, MATHY-HARTET M *et al.*: In vitro effects of aceclofenac and its metabolites on the production by chondrocytes of inflammatory mediators. *Inflamm. Res.* (2001) 50:391-399.
8. LINDBURY P, VOJNOVIC I, WARNER T: COX-2/COX-1 selectivity of aceclofenac in comparison with celecoxib and rofecoxib in the human whole blood assay. *Osteoarthr. Cartil.* (2000) 8(Suppl. B):S40-S41.
9. GRAU M, GUASCH J, MONTERO J *et al.*: Pharmacology of the potent new non-steroidal anti-inflammatory agent aceclofenac. *Arzneim-Forsch* (1991) 41:1265-1276.
10. ARAÑÓ A, ZAPATERO MI, BASI N, DUQUE A, GROPPER S: Comparison of the anti-inflammatory effect and gastrointestinal tolerability of aceclofenac and diclofenac. *Arzneim-Forsch* (1996) 46:398-400.
11. CREAMER J: A comparison of the pharmacokinetics of single and repeated doses of aceclofenac in young and elderly volunteers. *Br. J. Clin. Res.* (1992) 3:99-107.
12. CREMA A, CREMA F, PARNHAM MJ *et al.*: Effect of food on the bioavailability of aceclofenac tablets in healthy volunteers. *Eur. J. Clin. Res.* (1995) 7:155-160.
13. BORT R, PONSODA X, CARRASCO E *et al.*: Metabolism of aceclofenac in humans. *Drug Metab. Dispos.* (1996) 24:834-841.
14. OLIVIERA SA, FELSON DT, REED JI *et al.*: Incidence of symptomatic hand, hip and knee osteoarthritis among patients in a health management organisation. *Arthritis Rheum.* (1997) 38:1134-1141.
15. SANGHA O: Epidemiology of rheumatic disease. *Rheumatology* (2000) 39(Suppl. 2):3-12.
16. PERROT S, MENKES CJ: Nonpharmacological approaches to pain in osteoarthritis. Available options. *Drugs* (1996) 52:21-26.
17. WARD DE, VEYS EM, BOWDLER JM, ROMA J: Comparison of aceclofenac with diclofenac in the treatment of osteoarthritis. *Clin. Rheumatol.* (1995) 14:656-662.
18. DIAZ C, RODRIGUEZ A, GELI C, LLOBET JM, TAPOUNET R: Comparison of aceclofenac and diclofenac in osteoarthritic pain. *Curr. Ther. Res.* (1988) 44:252-258.
19. DIAZ C, RODRIGUEZ DE LA SERNA A, GELI C, GRAS X *et al.*: Efficacy and tolerability of aceclofenac versus diclofenac in the treatment of knee osteoarthritis: a multicentre study. *Eur. J. Rheumatol. Inflamm.* (1996) 16:17-22.
20. PEREZ BUSQUIER M, CALERO E, RODRIGUEZ M *et al.*: Comparison of aceclofenac with piroxicam in the treatment of osteoarthritis. *Clin. Rheumatol.* (1997) 16:154-159.
21. TORRI G, VIGNATI C, AGRIFOGLIO E *et al.*: Aceclofenac versus piroxicam in the management of osteoarthritis of the knee: a double-blind controlled study. *Curr. Ther. Res.* (1994) 55:576-583.
22. KORNASOFF D, FRERICK H, BOWDLER J, MONTULL E: Aceclofenac is a well-tolerated alternative to naproxen in the treatment of osteoarthritis. *Clin. Rheumatol.* (1997) 16:32-38.
23. SYMMONS DP: Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. *Best Pract. Res. Clin. Rheumatol.* (2002) 16:707-722.
24. MARTIN-MOLA E, GIJÓN-BAÑOS J, ANSOLEAGA JJ: Aceclofenac in comparison to ketoprofen in the treatment of rheumatoid arthritis. *Rheumatol. Int.* (1995) 15:111-116.
25. 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.
26. PASERO G, MARCOLONGO R, SERNI U, PARNHAM MJ, FERRER F: A multicentre, double-blind comparative study of the efficacy and safety of aceclofenac and diclofenac in the treatment of rheumatoid arthritis. *Curr. Med. Res. Opin.* (1995) 13:305-315.
27. KORNASOFF D, MAISENBACHER J, BOWDLER J, RABER A: The efficacy and tolerability of aceclofenac compared to indomethacin in patients with rheumatoid arthritis. *Rheumatol. Int.* (1996) 15:225-230.
28. PEREZ-RUIZ F, ALONSO-RUIZ A, ANSOLEAGA JJ: Comparative study of the efficacy and safety of aceclofenac and tenoxicam in rheumatoid arthritis. *Clin. Rheumatol.* (1996) 15:473-477.
29. HUSKISSON EC, IRANI M, MURRAY F: A large prospective open-label, multicentre SAMM study, comparing the safety of aceclofenac with diclofenac in patients with rheumatic disease. *Eur. J. Rheumatol. Inflamm.* (2000) 17:1-7.
30. VILLA-ALCÁZAR LF, DE BUERGO MA, LENZA HR, FRUITÓS EM, Spanish Study Group on Aceclofenac in Ankylosing Spondylitis: Aceclofenac is as safe and effective as tenoxicam in the treatment of ankylosing spondylitis: a 3 month multicenter comparative trial. *J. Rheumatol.* (1996) 23:1194-1199.
31. PASERO G, RUJU G, MARCOLONGO R *et al.*: Aceclofenac versus naproxen in the treatment of ankylosing spondylitis: a double-blind, controlled study. *Curr. Ther. Res.* (1994) 55:833-842.
32. BATLLE-GUALDA E, FIGUEROA M, IVORRA J, RABER A: The efficacy and tolerability of aceclofenac in the treatment of patients with ankylosing spondylitis: a multicenter controlled clinical trial. Aceclofenac-Indomethacin Study Group. *J. Rheumatol.* (1996) 23:1200-1206.
33. CECCHETTIN M, CEREA P, TORRI G: Therapetic efficacy of aceclofenac and diclofenac in acute knee arthroses. *Clin. Trials J.* (1988) 25:144-151.
34. ANDERSSON GBJ: Epidemiology of low back pain. *Acta Ortho. Scand.* (1998) 69(Suppl.):28-31.
35. AGRIFOGLIO E, BENVENUTI M, GATTO P *et al.*: Aceclofenac: a new NSAID in the treatment of acute lumbago. Multicentre single-blind study versus diclofenac. *Acta Ther.* (1994) 20:33-45.
36. SCHATTENKIRCHNER M, MILACHOWSKI KA: A double-blind, multicentre, randomised clinical trial comparing the efficacy and tolerability of aceclofenac with diclofenac resinate in patients with acute low back pain. *Clin. Rheumatol.* (2003) 22:127-135.
37. YSCLA A: Aceclofenac and paracetamol in episiotomal pain. *Drugs Exp. Clin. Res.* (1988) 14:491-494.
38. MOVILIA PG: Evaluation of the analgesic activity and tolerability of aceclofenac in the treatment of post-episiotomy pain. *Drugs Exp. Clin. Res.* (1989) 15:47-51.
39. BUBANI G: The analgesic activity and tolerability of aceclofenac in the treatment

of odontalgia: a double-blind placebo-controlled evaluation. *Clin. Trials J.* (1988) 25:244-253.

40. SAINZ-OLALLA F: Analgesic efficacy of aceclofenac: double-blind controlled study versus placebo in odontalgia. *Curr. Ther. Res.* (1988) 43:900-902.

41. PUIGVERT TORRENT A: Dose-response study of the analgesic activity of aceclofenac in odontalgia following extraction of the third molar. *Drug Invest.* (1990) 2:132-136.

42. DA FONSECA AM, BAGNOLI VR: A multicentre study of the efficacy and tolerability of aceclofenac in the treatment of primary dysmenorrhoea. *Rev. Bras. Med.* (1999) 56:169-173.

43. KÖBERLE G, COUTO MAGALHAES AA, JANSEN PACCOLA CA *et al.*: Multicentre, open study of the use of aceclofenac 100 mg, twice a day, in the treatment of muscular-skeletal traumas. *Rev. Bras. Med.* (1998) 55:63-69.

44. ISHIDA A, ADAMES MK: Study of the efficacy and tolerability of aceclofenac in the treatment of post-traumatic acute process in orthopaedics and traumatology. *Rev. Bras. Med.* (1997) 54:687-693.

45. CALIN A, MURRAY FE: Aceclofenac: side effects and safety. *Eur. J. Rheumatol. Inflamm.* (1996) 16:13-16.

46. PERIS F, BIRD HA, SERNI U *et al.*: Treatment compliance and safety of aceclofenac versus standard NSAIDs in patients with common arthritic disorders: a meta-analysis. *Eur J. Rheumatol. Inflamm.* (1996) 16:37-45.

47. YANAGAWA A, ENDO T, KUSAKARI K, KUDO T, SHIMADA J, MIZUSHIMA Y: Endoscopic evaluation of aceclofenac-induced gastroduodenal mucosal damage: a double-blind comparison with sodium diclofenac and placebo. *Jpn J. Rheumatol.* (1998) 8:249-259.

48. 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.

49. LLORENTE MELERO MJ, TENIAS BURILLO JM, ZARAGOZA MARCET A: Comparative incidence of upper gastrointestinal bleeding associated with individual non-steroidal anti-inflammatory drugs. *Rev. Esp. Enferm. Dig.* (2002) 94:7-18.

50. LEMMEL E-M, LEEB B, DE BAST J, ASLANIDIS S: Patient and physician satisfaction with aceclofenac: results of the European Observational Cohort Study. *Curr. Med. Res. Opin.* (2002) 18:146-153.

51. PERIS F, MARTÍNEZ E, BADIA X, BROSA M: Iatrogenic cost factors incorporating mild and moderate adverse events in the economic comparison of aceclofenac and other NSAIDs. *Pharmacoeconomics* (2001) 19:779-790.

52. EVANS C: The use of consensus methods and expert panels in pharmacoeconomic studies: practical applications and methodological limitations. *Pharmacoeconomics* (1997) 12:121-129.

53. LANE NE, THOMPSON JM: Management of osteoarthritis in the primary-care setting: an evidence-based approach to treatment. *Am. J. Med.* (1997) 103(Suppl. 6A):25-30.

54. CREAMER P, HOCHENBERG MC: Osteoarthritis. *Lancet* (1997) 350:503-509.

Affiliation

Professor Erik Legrand
Service Rheumatologie, CHU Angers,
4 rue Larrey 49933, Angers Cedex 9, France
Tel: +33 2 41 35 35 72;
Fax: +33 2 41 35 37 00;
E-mail: erlegrand@chu-angers.fr