

# Nimesulide for painful osteoarthritis

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Osteoarthritis is one of the most common joint disorders in the world. It is costly and a major cause of pain and disability, especially in the elderly. The severity of pain often calls for treatment with nonsteroidal anti-inflammatory drugs. Worldwide experience with nimesulide shows that this nonsteroidal anti-inflammatory drug has a number of pharmacological properties that may make it favorable in the treatment of joint diseases. In recent years, several controlled studies have been carried out in order to investigate its analgesic effects in patients with OA. The objective of this article is to review some of the features of osteoarthritis and to identify the role of nimesulide as a drug particularly tailored for the treatment of painful osteoarthritis.

Osteoarthritis (OA) is one of the most common forms of musculoskeletal disorder encountered worldwide, particularly in Western populations. A recent WHO report on the global burden of disease indicates that OA is likely to become one of the most important causes of disability in both women and men [1]. The prevalence of OA increases with age, affecting a large proportion of elderly people [2]. It affects over 50% of the population over 65 years of age and 80% of the population over 75 years of age [3]. Annual arthroplasty rates in Europeans over the age of 65 years are around 0.5–0.7 per 1000 [4], representing a significant cost to society.

The main characteristic of OA is a slowly developing degenerative breakdown of cartilage, with episodic inflammation of the synovium. OA affects all structures within a joint; pathological changes also occur in the synovium, bone, and many other joint structures [5]. Pain is the most prominent and disabling symptom in patients with OA [6,7], and local inflammation in the synovium and the cartilage may significantly contribute to its development and joint damage.

To date, no drugs have shown a clear disease-modifying efficacy in OA [8]. Nutritional supplements, in particular glucosamine and chondroitin-sulfate, are frequently used by patients. However, the therapeutic value of these compounds in the treatment of painful OA is still controversial [9]. The treatments currently available to alleviate OA symptoms are nonpharmacological (e.g., patient education, aerobic and muscle-strengthening exercise, lifestyle changes and weight control) and pharmacological methods [3,10]. The latter are based on the administration of pure analgesics such as paracetamol, which is to be considered the first-line drug according to the European League against

Rheumatism (EULAR) [4] and the American College of Rheumatology (ACR) Recommendations [11]. However, the severity of pain often requires treatment with nonsteroidal antiinflammatory drugs (NSAIDs), which are the drugs preferred by many patients with OA [12]. Indeed, NSAIDs are the drug most commonly used by many doctors for the management of pain in OA patients, in comparison to simple analgesics [12,13]. In clinical practice, OA should be regarded as a phasic disease and thus the short-term administration of NSAIDs during OA flares (episodic exacerbations of inflammation and pain) is a good therapeutic option for the majority of patients [3,13]. A number of NSAIDs are available for the treatment of OA. In recent years, the pharmacological management of OA was dominated by highly selective cyclooxygenase (COX)-2 inhibitors, until some compounds of this class were withdrawn due to concerns surrounding their cardiovascular tolerability profile [14–16]. This event was followed by a renewed interest for the agents already available in the market before the introduction of COX-2 inhibitors.

## Nimesulide

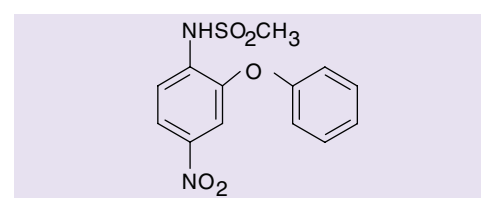
Nimesulide is a NSAID indicated for the treatment of acute pain, the symptomatic treatment of painful OA and primary dysmenorrhea. This review will focus on the role of nimesulide in the treatment of painful OA.

## Chemistry & development

Nimesulide is a nonacidic NSAID with a pKa of 6.5. Its chemical name (4-nitro-2-phenoxyethanesulfonanilide) was the basis for the generic name of the drug – nimesulide. The chemical structure, related to the sulfonanilide class, is shown in Figure 1.

**Keywords:** nimesulide,  
nonsteroidal anti-  
inflammatory drugs,  
osteoarthritis, pain

future  
medicine

**Figure 1. Nimesulide.**

Nimesulide differs from other nonsteroidal anti-inflammatories in that its chemical structure contains a sulfonanilide moiety as the acidic group. It is known as: methane-sulfonamide, N-(4-nitro-2-phenoxyphenyl)-, or 2-phenoxy-4-nitro-methanesulfonanilide, or 4-nitro-2-phoxymethanesulfonanilide.

The discovery of this compound (originally named R-805) arose from investigations performed at Riker Laboratories Inc. (Northridge, CA, USA), later part of the 3M Company at St Paul, MN, USA. The molecule was synthesized in early 1971. It is interesting to note that the synthesis of nimesulide slightly preceded the first hypothesis suggested by Sir John Vane and his colleagues on the mechanism of action of aspirin and related drugs. In 1980, Helsinn Healthcare (Switzerland), acquired the worldwide licensing rights for nimesulide. The drug was first marketed in Italy in 1985.

#### Pharmacodynamics

As expected for a NSAID, the therapeutic effects of nimesulide are largely related to its ability to reduce prostaglandin synthesis by inhibiting COX enzymes. With regard to this mechanism of action, evidence exists indicating that nimesulide may be defined as a preferential inhibitor of COX-2; indeed, at therapeutic concentrations, nimesulide shows a five- to 50-fold selectivity for COX-2 over COX-1 [14–18]. Moreover, nimesulide displays several pharmacodynamic properties, which may explain the anti-inflammatory and analgesic effects of this drug [19]; these properties include reduced generation of superoxide anions by stimulated polymorphonuclear leukocytes (PMN), inhibition of histamine release from mast cells and basophils, inhibition of phosphodiesterase (PDE) IV, inhibition of the production of platelet-activating factor (PAF), scavenging of hypochlorous acid, reduction of the synthesis of matrix metalloproteases (MMPs), reduction of apoptotic processes in chondrocytes and other connective tissue cells, and reduction of the activity of nitric oxide synthases (NOS).

The ability of nimesulide to affect so many mediators involved in the inflammatory process provided it with a rather unique role of multi-acting drug in several inflammatory pain conditions. In addition, the sparing of inhibition of the physiologically important COX-1 prostanooids in the gastrointestinal (GI) tract has been shown to be related to the low incidence of serious GI adverse events associated with the use of this drug [20–23].

#### Pharmacokinetics & metabolism

The pharmacokinetic properties of nimesulide have been largely investigated [24,25]. The drug has a fast rate of oral absorption and the presence of food did not reduce either the rate or extent of nimesulide absorption. After administration of 50–200 mg tablets to healthy volunteers, mean maximum plasma concentration ( $C_{max}$ ) values ranging 1.98–9.85 mg/l were achieved within 1.67–3.17 h ( $t_{max}$ ). Similar  $C_{max}$  values were observed for nimesulide 100–200 mg in granule (sachets) or suspension formulation, whereas the  $t_{max}$  was shorter (1.22–2.08 h) for these formulations in comparison with tablets. After repeated oral administration of 100 mg tablets twice daily for 10 days, the mean  $C_{max}$  and  $t_{max}$  at steady-state were similar to those observed after a single dose. All oral formulations demonstrate high and equivalent bioavailability. Elimination is progressive, with the half-life in plasma being 2–5 h for the parent drug and 3–9 h for its main metabolite (4-hydroxynimesulide, M1); this allows for convenient twice-daily dosage without any evidence of accumulation with the recommended 100 mg dose.

Like other NSAIDs, nimesulide is extensively bound to plasma proteins (albumin); the unbound fraction in plasma is approximately 1%. The drug is rapidly distributed into the synovial fluids and accumulates there at effective concentrations [26].

It is metabolized via liver cytochrome P450 (CYP)2C9, 2C19 and possibly 1A2, principally to the 4-hydroxy-metabolite, which has pharmacological properties similar to those of the parent drug. All metabolites are then excreted in the urine (~70%) and feces (~20%).

No interactions of clinical relevance between nimesulide and other drugs, such as glibenclamide, cimetidine, antacids, furosemide, theophylline and digoxin, have been observed; however, as for other NSAIDs, the concomitant administration of nimesulide and warfarin as well as other NSAIDs is not recommended.

Age, gender or moderate renal impairment do not influence the elimination of the drug; dosage adjustment is not necessary in these categories. Nimesulide is contraindicated in patients with hepatic impairment.

#### Efficacy & safety in osteoarthritis

Data from the most relevant studies in which the effects of nimesulide have been compared with those of active comparator drugs in patients with OA will now be reviewed.

A multicentric dose-finding study was carried out in 329 patients with OA divided into four groups, who received nimesulide 50, 100 or 200 mg twice daily or placebo, for 1 month [27]. This study showed a dose-effect relationship for nimesulide and supported the view that the optimal dose of nimesulide for efficacy is 100 mg twice daily.

Huskisson and colleagues compared nimesulide with diclofenac in an active control equivalence study during a 24-week period [28]. A total of 279 patients with OA of the hip or knee received either nimesulide 100 mg twice daily or diclofenac 50 mg three-times daily. Global efficacy and the Lequesne Functional index were the primary efficacy measures. At the end of the treatment period, nimesulide proved to be at least as effective as diclofenac, but with a statistically significant superiority for GI tolerability.

By evaluating pain and functional parameters, Porto and colleagues found nimesulide 100 mg twice daily and diclofenac 50 mg three-times daily for 1 month equally effective in a parallel group study in 89 patients with OA of the hip or knee [29]. At the end of the study period, the endoscopic evaluation proved normal in the majority of patients, although three patients in the diclofenac group developed ulcers, compared with only one in the nimesulide group.

Kriegel and colleagues compared nimesulide (100 mg twice daily) with naproxen (250 mg in the morning and 500 mg at night) in a double-blind study lasting 1 year [30]. While efficacy was rated similarly as good/excellent by investigators for both drugs (59.3% for nimesulide and 56.4% for naproxen), patients treated with nimesulide showed a lower incidence of GI adverse events.

Similar results were obtained by Quattrini and Paladin, in a study comparing nimesulide 100 mg twice daily with naproxen 500 mg twice daily, where both drugs demonstrated equal effectiveness after 4 weeks of treatment [31].

The efficacy and tolerability of nimesulide (200 mg/day) was also compared with those of etodolac (600 mg/day) in 199 patients with OA of the knee over a period of 3 months [32]. In this multicenter study, both the beneficial and unwanted effects of the two drugs were generally comparable, although overall judgements of the efficacy by both the physicians and the patients were in favor of nimesulide.

A meta-analysis of 6 trials with OA patients was carried out to evaluate the efficacy and safety of nimesulide in comparison with placebo and other NSAIDs (diclofenac, naproxen, piroxicam, ketoprofen and etodolac). Results showed that the efficacy of nimesulide was superior to placebo and at least comparable to that of the other NSAIDs, with a trend of better tolerability [33].

Based on the evidence that nimesulide is an effective NSAID and could be considered as a drug of choice for the symptomatic treatment of OA, a prospective, randomized, double-blind study has been performed to specifically compare the analgesic efficacy of nimesulide, celecoxib and rofecoxib in 30 patients with knee OA, over a period of 3 weeks [34].

Using this design, each drug was tested against all the others and was administered equally either as first, second or third in the sequence to the same number of patients. Enrolled patients were randomly assigned to treatment with single oral doses of nimesulide 100 mg, celecoxib 200 mg or rofecoxib 25 mg. Each drug was given daily for 7 days. As patients with OA have pain that typically increases with activity and is particularly evident after a period of inactivity, special attention was devoted to the onset of the action on pain connected with movement after the drug administration in the morning. The main efficacy criterion was pain intensity assessment by using the visual analog scale (VAS) measured on a scale of 0–100 mm. In addition, at the end of each week of treatment patients answered questions about analgesic efficacy on a five-point categorical scale: none, mild, moderate, good and very good. At the end of the study, each patient was asked about which of the three forms of treatment he or she would opt for as a continuation of the therapy.

Although all the drugs induced a reduction in pain intensity, the analgesic efficacy of nimesulide was clearly superior to that of the other two NSAIDs. In addition, it is particularly worth underlining that the analgesic action of nimesulide was more rapid than that exerted by the other drugs tested. In fact, only the patients

treated with nimesulide recorded mean VAS values measured 15 and 30 min after drug intake, which differed significantly from those measured in basal conditions.

This observation appears to be of particular importance if we consider that a rapid decrease in pain intensity will make a considerable difference in the ability of patients with OA to carry out their normal everyday activities.

The percentage of patients who reported good or very good analgesic efficacy were 53.4% in the nimesulide group, 46.7% in the celecoxib group, and 50.0% in the rofecoxib group. The percentage of patients who reported good or excellent tolerability were 76.7% in the nimesulide-treated group, 70.0% in the celecoxib-treated group and 76.7% in the group of patients treated with rofecoxib.

In conclusion, this personal experience with nimesulide in patients with knee OA has proved the suitability of this drug in this clinical setting, where a fast onset of analgesic activity is also desirable.

Further details on the efficacy and tolerability of nimesulide in clinical trials may be found in a comprehensive monograph published recently (see: Information resources).

#### Postmarketing surveillance

A postmarketing survey was carried out in Italy in 22,938 patients to assess the efficacy and tolerability of nimesulide in the short-term treatment of OA [35]. The treatment period ranged from 1 to 3 weeks. At the end of the study, physician's overall evaluation indicated that 76% of patients showed good/optimal response to the treatment. Patients' evaluations were similarly positive: 69% of patients evaluated their condition as good/excellent.

Adverse reactions (ARs), presumably related to nimesulide, occurred in 8% of patients; dyspepsia, pyrosis and nausea accounted for approximately 90% of events, and no serious complications such as peptic ulceration and/or gastrointestinal bleeding were observed.

The safety profile of the drug is constantly assessed through an accurate postmarketing surveillance (PMS), critically followed up at Helsinn Healthcare (Switzerland). From 1985 to June 2006, over 480 million patients have been treated with nimesulide worldwide; the features of the events recorded by the PMS, together with the evidence from clinical studies, suggest that the benefit/risk profile of nimesulide remained favorable and unchanged over time.

#### Regulatory affairs

Nimesulide is available as tablets, granules (sachets), suppositories, oral suspension, drops and topical gel. Original nimesulide is marketed worldwide in more than 50 countries, mainly in Europe, Central and Latin America and Asia, with the following authorized tradenames: Ainex<sup>®</sup>, Aulin<sup>®</sup>, Donulide<sup>®</sup>, Eskafam<sup>®</sup>, Heugan<sup>®</sup>, Mesulid<sup>®</sup>, Nexen<sup>®</sup>, Nimed<sup>®</sup>, Nimedex<sup>®</sup>, Nisulid<sup>®</sup>, Scafam<sup>®</sup> and Scaffan<sup>®</sup>.

According to the last Summary of Product Characteristics (2003), nimesulide is approved for use in the treatment of acute pain, in the symptomatic treatment of painful osteoarthritis and in primary dysmenorrhoea.

As for other NSAIDs, the use of nimesulide is recommended for the shortest time needed to solve the symptoms of inflammation.

#### Conclusion

OA is the most common form of arthritis. Typical symptoms of OA are pain and functional limitation. Treatment of symptomatic OA is focused on controlling the pain and improving the patient quality of life. There is abundant evidence that anti-inflammatory drugs are more effective than simple analgesics; this is not surprising since there is also considerable evidence for the role inflammation plays in OA. Indeed, very often, the joints of patients affected by OA show cardinal signs of inflammation like warmth and swelling. There is a very large experience of the use of the NSAID nimesulide in OA from around the world. A considerable number of studies clearly show that nimesulide in its convenient dosing schedule of 100 mg twice daily is at least as effective as other NSAIDs with which it has been directly compared. A comprehensive analysis of these data suggest that nimesulide represents an effective agent for the treatment of OA pain, with particular reference to the rapid onset of its analgesic effect. This aspect is of particular importance if one considers that a rapid decrease in pain intensity will contribute importantly to the ability of patients with OA to carry out their normal everyday activities. In addition, the good tolerability profile, with special regard to gastrointestinal effects, may offer a significant advantage over other NSAIDs. It is clear, however, that even with a well-tolerated drug like nimesulide, caution is required to ensure the safety of patients who are more vulnerable, such as the elderly and those with hepatic impairment.

**Future perspective**

Two main objectives of the pharmacological management of OA are the resolution or the relief of pain, and the prevention of the progression of the disease by reducing the degradation of joint cartilage. NSAIDs are very useful in the treatment of symptomatic OA. Nimesulide proved to be more rapid and effective in providing symptomatic relief than did some COX-2 selective inhibitors [27,34,36].

However, NSAIDs are considered as lacking a structure-modifying effect. This means that they can reduce pain and functional limitation, but not the progression of joint deterioration. Recent data demonstrate that nimesulide has a favorable effect on the metabolism of joint cartilage that is unrelated to COX-inhibition [37,38], suggesting that this drug may also positively affect the natural course of OA. Further studies are needed to clarify the possible differences among the various NSAIDs with reference to this particular action.

**Information resources***Relevant further reading*

Rainsford KD: Nimesulide. Actions and Uses. Birkhäuser Verlag, Basel, CH, Switzerland (2005).

- Comprehensive monograph on nimesulide recently published.

*Relevant websites*

- Nimesulide Information [www.nimesulide.net](http://www.nimesulide.net)
- The arthritis foundation [www.arthritis.org](http://www.arthritis.org)
- Bone and Joint decade online [www.boneandjointdecade.org](http://www.boneandjointdecade.org)
- The European League Against Rheumatism [www.eular.org](http://www.eular.org)
- National Institute of Arthritis and Musculoskeletal and skin diseases [www.nih.gov/niams](http://www.nih.gov/niams)
- American College of Rheumatology [www.rheumatology.org](http://www.rheumatology.org)

**Executive summary****Mechanism of action**

- Nimesulide prevents the generation of prostaglandins by inhibiting cyclooxygenase (COX) enzymes, with preferential action on COX-2.
- Moreover, it inhibits the production, release or activity of a number of mediators of inflammatory pain.
- Recent data suggest that nimesulide may positively affect the metabolism of joint cartilage.

**Pharmacokinetic properties**

- Following oral administration, nimesulide (50–200 mg) is rapidly and extensively absorbed. Mean maximum plasma concentration ( $C_{max}$ ) values ranging 1.98–9.85 mg/l are achieved within 1.67–3.17 h ( $t_{max}$ ) from drug intake (tablets); similar  $C_{max}$  values, but lower  $t_{max}$  are reached with granule formulation.
- The half-life in plasma is approximately 2–5 h for the parent drug and 3–9 h for its main metabolite, thus enabling convenient twice-daily dosage.
- Metabolism involves the liver cytochrome P450 (CYP) system. The drug is metabolized by CYP2C9 and CYP2C19 (and possibly CYP1A2), principally to the 4-hydroxy-metabolite (M1). This metabolite has similar pharmacological properties to the parent drug, although with lower efficacy.
- Excretion in the urine and feces accounts for approximately 70% and 20% of the administered dose, respectively.
- Age, gender or moderate renal impairment do not influence the elimination pattern of the drug.
- The use of nimesulide is contraindicated in patients with hepatic impairment.

**Clinical efficacy & safety**

- Nimesulide has been directly compared with the most widely used drugs for the treatment of painful osteoarthritis (OA).
- The most convenient dosing schedule is 100 mg twice daily.
- Nimesulide proved to be a valid alternative to other nonsteroidal anti-inflammatory drugs (NSAIDs) with a similar or even superior analgesic efficacy characterized by a fast onset of action.
- Nimesulide demonstrated a good safety profile in OA patients, at least comparable to that of the most used NSAIDs, with evidence of a better gastrointestinal tolerability.

**Drug interaction**

- No interactions of clinical relevance between nimesulide and many other drugs have been observed; the concomitant administration of nimesulide and warfarin as well as other NSAIDs is not recommended.

**Dosage & administration**

- Nimesulide is available in tablets, granules (sachets), suppositories, oral suspension, drops and topical gel.
- Recommended dosing schedule (adults and children >12 years old) for tablets/granules: 100 mg twice daily.
- Recommended dosing schedule for suppositories: 200 mg twice daily.
- The presence of food does not influence either the rate or extent of nimesulide absorption.

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