**COMMENTARY**

Nimesulide – a multifactorial approach to inflammation and pain: scientific and clinical consensus

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**ABSTRACT**

*Background:* This paper summarises the outcome from a consensus meeting, held in Rome on 5 October 2005, that aimed to review the state of the art regarding the non-steroidal anti-inflammatory drug (NSAID) nimesulide, with reference to its chemical, pharmacokinetic, pharmacological and clinical characteristics.

*Scope:* The meeting aimed to provide a continuous and up-to-date evaluation of the clinical and safety profile of nimesulide, and of its role in the treatment of inflammatory pain, in light of existing therapeutic alternatives, through a revision and critical discussion on the information available on the drug among authoritative experts in different fields of medical science.

*Findings:* The members of the Consensus Report Group on Nimesulide (CRGN) recognised that nimesulide is an NSAID which exerts its analgesic, anti-inflammatory and antipyretic activities thanks to unique chemical and pharmacokinetic characteristics, and to a multifactorial mechanism of action, which goes beyond its preferential inhibitory activity on the COX-2 enzyme. Nimesulide was found to be at least as effective, or superior, to placebo and other NSAIDs, with a particularly fast onset of analgesic action. The safety profile is in line with that expected from the class, with evidence of a better gastrointestinal safety profile.

*Conclusions:* Based on the available evidence, the CRGN concluded that nimesulide remains an effective and safe therapeutic choice for the treatment of various painful inflammatory conditions, with a rapid onset of analgesic activity and an overall positive benefit/risk profile.

**Introduction**

The use of non-steroidal anti-inflammatory drugs (NSAIDs) plays a fundamental role in controlling inflammation and in pain relief. These drugs inhibit the production of prostaglandins (PGs) through the inhibition of COX-1 and COX-2, the enzymes responsible for PG synthesis. However, studies in experimental models and clinical investigations have clearly demonstrated other activities on pro-inflammatory mediators involved in NSAID action in providing relief from inflammation and pain.

Although NSAIDs differ in pharmacokinetic, pharmacological, pharmacodynamic and clinical profile, they have essentially the same therapeutic properties, and share the most important side effects.

Gastrointestinal (GI) adverse events remain the main concern in the use of NSAIDs and GI tolerability is a central issue for clinicians who prescribe these drugs. Other important side effects should also be taken into...
consideration when prescribing NSAIDs such as allergic reactions, skin reactions, renal complications, alteration of hepatic enzyme levels and rarely hepatopathies. Recent concerns due to an apparent higher incidence of cardiovascular (CV) adverse events with the newer NSAIDs, the coxibs, posed some questions on the CV safety profile of the whole class.

To date, the scale of side effects is a key discriminator for choosing between one NSAID and another.

This paper provides an overview on the state of the art of the NSAID nimesulide through a consensus agreement about its therapeutic uses, safety and actions, obtained from a meeting of leading international authorities held in Rome on 5 October 2005. The meeting was comprised of experts and opinion leaders in a number of scientific disciplines such as chemistry, pharmacology and different branches of medicine, here quoted as members of the Consensus Report Group on Nimesulide (CRGN).

Nimesulide is an NSAID with analgesic, anti-inflammatory and anti-pyretic characteristics, with unique chemical and pharmacokinetics features and a multifactorial mechanism of action, which goes beyond its preferential inhibitory activity on the COX-2 enzyme, as demonstrated in studies in animal and human models.

Evidence supports the clinical efficacy and safety of the drug in the treatment of acute pain, painful osteoarthritis and primary dysmenorrhoea.

During the meeting, the members of the CRGN critically reviewed the information on the drug through an evidence-based approach which involved the evaluation of available published randomised controlled clinical trials, including publications in the PubMed database, World of Science (ISI) and Chemical Abstracts, and unpublished laboratory and clinical data regarding nimesulide. Although most of the publications were in English, some in other major languages were also considered. A summary of the available records was prepared and distributed to all participants who critically reviewed the key chemical, biochemical, pharmacological and toxicological papers from the peer reviewed literature and gave their feedback to the chairman. Members of the CRGN were also given other information in the form of a recently published comprehensive monograph on nimesulide which represents an exhaustive collection of evidence from a vast amount of literature on the drug. In addition, the members of CRGN were also updated on the approved status of nimesulide in the European Union as stated by the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA; now the European Medicines Agency, EMA) in 2003. Subsequently, the consensus statements, as presented in this paper, have been submitted to all members of the Committee and their approval obtained.

Nimesulide was invented by Dr George Moore (Figure 1) (who can be considered the ‘father’ of nimesulide) and a group of colleagues at 3M Biochemical Research Laboratory, which was merged into Riker Laboratories, when the latter was acquired by 3M Co. The discovery of nimesulide slightly preceded the discovery of cyclo-oxygenase and of the key roles of prostaglandins in inflammation and pain. The design rationale was based on the premise that free radicals are critical factors in chronic inflammatory disease and scavenging of these radicals might have novel anti-inflammatory activities in the control of chronic inflammatory conditions.

Following initial unsuccessful observations on fluoroalkane-sulfonanilides, Dr Moore and colleagues modified their strategy to incorporate a 4-nitro group into the sulphonanilide structure to achieve oxyradical scavenging, and this led to the synthesis of 4-nitro-2-phenoxymethane-sulfonanilide. Designated compound R-805, it was found to have the best therapeutic ratio compared with reference
NSAIDs available at that time. The chemical name of the compound, 4-Nitro-2-phenoxymethane-sulphonanilide, served as the basis for the generic name of the drug, i.e. nimesulide (Figure 2). With reference to the chemical structure, nimesulide belongs to the sulphonanilides which, as outlined in Figure 3, are a unique chemical category within NSAIDs.

In 1980, Helsinn Healthcare SA (Switzerland) licensed the molecule, acquiring the worldwide rights, and proceeded to invest widely in research on the drug. This gave a basis for enlarged registration and commercialisation of the drug and, furthermore, allowed the identification of the multifactorial basis for the actions of nimesulide.

The first country where nimesulide was licensed and marketed was Italy, in 1985. Subsequently, the drug has become the most prescribed and used NSAID in that country. It is now marketed in over 50 countries worldwide and in some is among the market leaders, if not the market leader itself.

Pharmacokinetics and drug interactions

Nimesulide has a fast rate of oral absorption (with peak plasma concentrations at 1–3 hours), related to the rapid onset of pain relief in a variety of painful inflammatory conditions. All oral formulations show high and equivalent bioavailability; good drug absorption from the topical gel and rectal suppository formulations is also obtained. The good absorption of the topical formulation was obtained by selecting a micronised form of nimesulide powder to facilitate homogeneous dispersion in a semi-solid (gel) form at the concentration of 3%. This formulation contains the typical excipients of gel preparation for cutaneous applications, such as to favour penetration of the gel in the cutaneous region requiring treatment.

Nimesulide is oxidatively metabolised via liver cytochromes P₄₅₀ (principally by CYP-2C9, CYP-2C19 and possibly CYP-1A2) mainly to the 4-hydroxy-metabolite (4-OH-NME) which has similar pharmacological properties to the parent drug, although its potency is lower. As for other NSAIDs, nimesulide is strongly bound to plasma proteins and has a moderately low volume of distribution. It is, however, rapidly distributed into the synovial fluids. This feature may account for the efficacy of the drug in controlling painful inflammatory reactions in osteoarthritis and other joint diseases. Elimination is progressive, with a half-life of 2–5 hours for the parent drug and 3–9 hours for its main metabolite (4-OH-NME), thus allowing for convenient 100 mg twice-daily dosage without any evidence of accumulation.

The elimination of the drug is not influenced by age, gender or moderate renal impairment (such as might be seen in the elderly) (Figures 4 and 5). The use of nimesulide is contraindicated in patients with hepatic impairment.

No clinically relevant drug–nimesulide interactions have been observed with the CYP inhibitor cimetidine or with warfarin, oral hyperglycaemic agents, antacids, digoxin, furosemide, theophylline or acenocoumarol.

Pharmacological properties

Nimesulide has a range of multifactorial actions in vitro, some of which have been demonstrated ex vivo.
or in vivo in patients. These are variously involved in the actions of this NSAID in controlling inflammation, pain and fever. It is the consensus view that the primary pharmacological action of nimesulide is to preferentially inhibit the cyclooxygenase-2 (COX-2) production of prostaglandins (especially PGE_2), the latter being major inflammatory mediators in controlling inflammation. In particular, nimesulide belongs to the group of NSAIDs shown to be 5 to 50-fold more selective for COX-2 than COX-1.

The sparing of inhibition of the physiologically important COX-1 prostanoids in organs such as the GI tract has been shown in both studies in human volunteers and experimental animal models to be conclusively related to the lower incidence of serious GI mucosal reactions (GI ulceration and bleeding) and GI adverse drug reactions (ADRs) that have been reported with the drug, in contrast to those that are frequently associated with other conventional NSAIDs (e.g. aspirin, indomethacin, naproxen, piroxicam).

Additionally, there is evidence from in vitro studies at pharmacological concentrations of the drug, as well as from some ex vivo and in vivo studies, that nimesulide has other actions that are known to be important in the inhibition of the inflammatory process (Figure 6). In particular:

- The inhibition of:
  - The release of histamine from mast cells and basophils.
  - Hydroxyl-radicals (which are scavenged), superoxide radicals (O_2^-) and the production of hypochlorous acid by activated polymorphonuclear neutrophil (PMN) leucocytes. Reduction in O_2^- and phagocytosis of PMNs has been shown ex vivo in healthy volunteers after administration of a standard dose of the drug.
  - Neutrophil adherence and expression of receptors (which have been observed at relatively high concentrations of the drug).
  - Phosphodiesterase (PDE) IV, with consequent increase in the intracellular levels of cyclic-3',5'-adenosine monophosphate (cyclic-AMP), which in turn may negatively regulate the release or production of histamine, as well as of leukotrienes, pro-inflammatory cytokines and enzyme release by leucocytes.
  - The production of platelet activating factor (PAF) from activated platelets and other cells.
  - Metalloproteinases (MMPs) which can cause the destruction of proteoglycans (PrGns), collagens and other components of connective tissue matrix in joints. Reduction in MMPs (especially stromelysin, or MMP-3) has been shown in the plasma of patients with degenerative joint diseases.

Figure 4. Nimesulide pharmacokinetic profile in the elderly does not differ from that in healthy young individuals. Each point represents data from a different study. CL/F = total plasma clearance; Vz/F = volume of distribution in the post-distribution phase.

Figure 5. Gender does not affect the rate and the extent of nimesulide absorption, nor the distribution and elimination parameters. Each symbol represents data from a different study. AUC = area under the concentration-time curve; AUCss = area under the concentration-time curve at steady state; C_{12} = plasma drug concentration 12 hours after administration; CL/F = total plasma clearance; C_{max} = peak plasma drug concentration; t_{max} = time to peak plasma drug concentration; t_{1/2,z} = apparent terminal life; Vd/F = apparent volume of distribution. (Reproduced from Bernareggi, with permission from Adis International)
Apoptotic process in chondrocytes and other connective tissue cells in osteoarthritis (OA)

- The activity of nitric oxide synthases (NOS) and the subsequent production of nitric oxide (NO) and peroxynitrite (ONOO⁻) from combination of NO with hydroxyl (OH•) radicals; these reactive oxygen species (ROS) being key mediators of the cellular destructive and inflammatory events in inflammation.

- The activation of glucocorticoid receptors leading to increased cellular activity of endogenous glucocorticoids is a potentially novel action of nimesulide that is not reported with other NSAIDs.

The ability of nimesulide to affect so many mediators involved in the inflammatory process provides it with the rather unique role of a multi-acting drug in different pathological conditions⁸⁻⁹.

**Clinical features**

Over 200 clinical trials evaluating the efficacy and safety profile of nimesulide have been conducted in more than 90 000 patients in a wide variety of acute and chronic inflammatory and painful conditions. In these controlled studies, nimesulide has been found to consistently show relief of painful inflammatory symptoms markedly superior to placebo and at least equivalent, or in some cases superior, to that of established NSAIDs (e.g. ibuprofen, naproxen, ketoprofen) and the newer class of highly selective COX-2 inhibitors or coxibs¹².

The critical and extensive scientific evaluation of the safety and efficacy of nimesulide by the CPMP in 2003² concluded that: (1) systemic formulations (oral 100 mg bid, rectal 200 mg bid) of nimesulide are effective in the treatment of acute pain, primary dysmenorrhea and symptomatic treatment of pain associated with OA; and (2) topical formulations of nimesulide are effective in the relief of pain associated with sprains and acute tendinitis. These recommendations have been supported by extensive clinical studies and evaluation of the current uses of the drug, and have now become the basis for the approved use of the drug in the EU and its recommended use worldwide.

**Treatment of acute pain**

Nimesulide is particularly indicated for the treatment of acute painful situations where acute inflammation is the most predominant component, such as soft tissue injuries, extra articular trauma, some ear, nose and throat inflammatory conditions (e.g. otitis), post-operative conditions and odontostomatological pain.

Several studies show that nimesulide is effective in the treatment of these conditions both compared with placebo and with the most widely used NSAIDs (e.g. naproxen, ibuprofen, diclofenac, mefenamic acid and celecoxib and rofecoxib). In these studies, nimesulide frequently showed superior or similar efficacy to the comparator drug and is characterised by a fast onset of analgesic action, evident 15 minutes after intake³⁻⁴ (Figure 7). The safety profile is comparable to reference compounds but with evidence of a better
overall GI tolerability both in terms of reported serious and non-serious events\(^{12,15-18}\). The good GI tolerability was also observed in long-term studies performed in OA patients\(^{12}\).

**Painful osteoarthritis**

A typical field of application of NSAIDs is the symptomatic treatment of painful osteoarthritis. According to the latest American College of Rheumatology guidelines (2000)\(^{19}\), NSAIDs could be considered as a valid alternative to the first-choice treatment, paracetamol, with particular reference to flare-ups when this first-choice treatment may give inadequate results. Nimesulide’s recommended indications and pharmacological profile are perfectly in compliance with these guidelines\(^{19}\).

In particular, some mechanisms of action of nimesulide, such as the inhibitory activity on COX-2 formation and activity, prevention of cartilage degradation\(^{20,21}\), the oxyradical scavenging activity and inhibitory activity on apoptosis\(^{11}\), give a credible basis for the use of nimesulide in osteoarthritis as well as other musculoskeletal joint diseases and trauma states\(^{12,15-17,20-24}\).

Besides the pharmacological rationale for its use in this particular condition, large amounts of data have been produced from several studies using different designs (placebo-controlled and double-blind studies)\(^{20-24}\).

Nimesulide has been demonstrated to significantly reduce the signs and symptoms of OA, with an efficacy at least comparable to the reference drugs (e.g. piroxicam, naproxen, diclofenac, ketoprofen, etodolac, celecoxib and rofecoxib)\(^{12,20-24}\) (Figure 8).

**Primary dysmenorrhoea**

Primary dysmenorrhoea affects a large proportion of menstruating women. The use of NSAIDs in the symptomatic treatment of primary dysmenorrhoea is particularly indicated as this pathological condition is directly linked to modification in prostaglandins. Clinical studies in more than 1400 women, over 1000 of whom were treated with nimesulide, widely document the activity of nimesulide in reducing pain from primary dysmenorrhoea\(^{12}\). Results showed nimesulide is more effective than placebo and other NSAIDs such as diclofenac, naproxen and mefenamic acid\(^{12}\). In particular, data showed the capability of nimesulide to act on intrauterine pressure and to induce the reduction of PGF\(_2\alpha\) (Figure 9), two key variables which play a fundamental role in the pain perception\(^{25}\). Nimesulide

![Figure 7. Anti-hyperalgesic effects of nimesulide 100 mg p.o. in comparison with diclofenac 50 mg p.o., celecoxib 200 mg p.o. and rofecoxib 25 mg p.o. in patients with rheumatoid arthritis. The onset of action for nimesulide is already evident 15 minutes after drug in-take. *p < 0.05 vs. baseline. (Reproduced from Bianchi and Broggini\(^{13}\), with permission from Blackwell Publishing)](image)

![Figure 8. Comparative efficacy of nimesulide versus diclofenac in the treatment of OA on hip and knee functionality in OA patients. A decrease in Lesquene index indicates an improvement in joint function. (Reproduced from Huskisson et al.\(^{22}\) with permission from Excerpta Medica Inc.)](image)
also showed a faster onset of action than the widely used NSAID, diclofenac, in relieving the pain from dysmenorrhoea, with symptoms being relieved within 30 minutes of drug ingestion\textsuperscript{26}, confirming previous results showing an onset of the analgesic effects of 19 minutes after drug intake\textsuperscript{12,25}.

Further clinical support is under development to maintain an up-to-date and documented efficacy profile of the drug in relevant inflammatory painful situations.

**Safety profile**

The review of the safety profile of nimesulide confirmed it to be, in general, similar to that for the class (Figure 10)\textsuperscript{2}. Although GI reactions, including dyspepsia and other non-serious complaints, are the most common for the NSAIDs class, there is evidence that nimesulide is better tolerated than other NSAIDs, with particular reference to GI ulceration, bleeding and intestinal perforation. In controlled clinical studies, including human and animal models, a large amount of data confirmed that the incidence of reported events of upper GI bleeding was very rare for the drug\textsuperscript{27,28}. Demonstration of this favourable GI safety profile is also evident from detailed molecular and cellular investigations that support the clinical profile\textsuperscript{27}. The combination of factors, including physico-chemical properties\textsuperscript{5,6} (being a near-neutral pKa compound in contrast to the conventional acidic NSAIDs), the sparing of COX-1 inhibition of GI protective PGs\textsuperscript{28}, control of histamine release and its actions on acid production and release of reactive oxygen species in the event of mucosal inflammation (e.g. by *Helicobacter pylori*) may all contribute to the low irritancy of this drug in the upper GI mucosa\textsuperscript{27–29}.

A recent multicentre population-based case-control study, which is one of the largest on upper gastrointestinal bleeding (UGIB) related to NSAIDs, found that nimesulide had one of the lowest risks for UGIB, comparable with ibuprofen and much lower than several commonly used NSAIDs such as piroxicam, ketoprofen and ketorolac, the latter two being among those NSAIDs with poor GI tolerability\textsuperscript{30}.

Nimesulide has shown to have a low incidence of renal reactions, in line with the pharmacokinetics of the drug. Other potential critical aspects which can influence the safety profile of nimesulide, such as skin and cardiovascular adverse events, are in line with that of the NSAID class\textsuperscript{2,27}. With particular reference to the cardiovascular safety profile of nimesulide, data from clinical trials and ADRs monitoring confirmed a low risk of cardiovascular events related to the use of the drug\textsuperscript{27}.

In patients with NSAID intolerance, nimesulide has been shown to be well tolerated. However, as with other NSAIDs, the drug is contraindicated in...
patients with history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to acetylsalicylic acid or other NSAIDs\textsuperscript{57}. Nimesulide has, however, been reported to be associated with hepatotoxicity (especially in Finland), although the pharmaco-epidemiological studies suggest this may be no more common than with other NSAIDs\textsuperscript{57}. Detailed evaluations of the potential factors associated with hepatotoxicity from nimesulide include concomitant intake of drugs that are known to be associated with hepatotoxicity (paracetamol, antibiotics, diclofenac, angiotensin-converting enzyme inhibitors), prior or concurrent liver or systemic inflammatory disease and intake of high doses beyond those recommended\textsuperscript{27,31}. A comprehensive and critical revision of all the efficacy and safety data available allows the conclusion to be made that the benefit/risk profile of nimesulide is positive and the risk of causing hepatic reactions is in line with that expected from the NSAID class, as confirmed by EMEA in 2003\textsuperscript{27,31}. This specific aspect was supported, among others, by an outcome from an independent epidemiological study, designed with the aim of evaluating the incidence of hepatic reactions due to use of NSAIDs in Italy\textsuperscript{27}. Besides confirming that the risk of hepatotoxicity for nimesulide and the whole NSAID class is very low, data showed there were no indications of an increased risk of hepatopathies and liver injuries for nimesulide compared to other NSAIDs. Although results suggested that there might be an association between the risk of serious liver injuries and nimesulide, the absolute risk was low and the differences between nimesulide and other NSAIDs, as well as differences between individual NSAIDs, were limited\textsuperscript{32}. This slight increase in risk does not alter the overall good nimesulide safety profile, especially if its GI safety profile is considered\textsuperscript{27-30}.

The safety profile of the drug is being constantly monitored through in-depth and accurate post-marketing surveillance which is critically followed up at Helsinn Healthcare SA. From 1985 through to June 2005, 2304 cases of adverse events with nimesulide have been received and recorded in the global database; there was a peak of reported cases coincident with the EMEA procedure which started decreasing immediately afterwards. From initial commercialisation up to June 2005, a total of 450 million treatment courses have been used, assuming nimesulide 100 mg bid as a daily dose and a mean treatment period of 15 days (Helsinn Healthcare SA, data on file).

Overall benefit/risk profile

Based on what is discussed here, the CRGN outlined some conclusions about the overall benefit/risk profile of the drug. The therapeutic benefits of nimesulide have been compared with both placebo and the most widely used NSAIDs for the main approved indications, including acute pain, treatment of painful osteoarthritis and primary dysmenorrhoea. Nimesulide proved to be a valid therapeutic alternative to other NSAIDs, with a similar or even superior clinical efficacy, characterised by a fast onset of the analgesic action.

Nimesulide shares the characteristic side effects of NSAIDs, such as GI, skin, renal and hepatic reactions. As for other drugs in the class, the occurrence of adverse reactions suggesting hypersensitivity comprises a significant proportion of the total. Analysis of the incidence of all adverse reactions from the available data confirms this to be in line with the class. In particular it can be affirmed that the incidence of upper GI perforation, bleeding and ulceration is low and that nimesulide is probably less prone to produce gastrointestinal bleeding than other NSAIDs. The incidence rate is similarly low for renal, serious skin and hepatic reactions.

Data from post-marketing surveillance confirm that there is no signal of any changes in the clinical characteristics of listed serious and non-serious adverse reactions over time or of any potentially ‘new’ adverse reactions or new signals related to nimesulide. This, together with the evidence from clinical studies, allows confirmation that the benefit/risk profile of nimesulide remains favourable and unchanged over time.

Summary of consensus statements

The opinion of the experts who have reviewed the evidence derived from clinical and experimental studies on nimesulide can be summarised as follows:

- Nimesulide has a unique chemical structure.
- Nimesulide demonstrates preferential COX-2 inhibitory activity, sparing COX-1 in most clinical models.
- Nimesulide shows unique broad actions on inflammatory processes.
- Nimesulide has a multi-factorial mode of action.
- Nimesulide’s pharmacokinetic profile shows rapid absorption by stomach and small bowel, favouring safe use in patients.
- Nimesulide has relatively few drug interactions.
- Nimesulide exerts its analgesic activity through central and peripheral actions.
- Nimesulide demonstrates rapid onset of action in the treatment of inflammatory pain.
• Nimesulide is proven to be effective in the treatment of acute pain states, i.e.:
  – Soft tissue injuries.
  – Extra-articular traumatism.
  – ENT inflammations.
  – Odonto-stomatological inflammatory pain.
  – Post-operative pain.
• Nimesulide is proven to be effective in the symptomatic treatment of pain in OA which could related to:
  – Reduced bio-marker indices reflecting cartilage degradation.
  – Inhibition of chondrocyte apoptotic processes.
  – Inhibition of COX-2 formation and activity.
  – ROS scavenging/inhibitory activity.
• Nimesulide is proven to be effective for the treatment of primary dysmenorrhoea due to its ability to diminished intrauterine pressure and PGF₂α level.
• Nimesulide’s safety profile can be described as follows:
  – Skin and hepatic safety profile in line with other NSAIDs.
  – Renal and CV adverse reactions very rare.
  – Superior GI safety profile versus other NSAIDs.

Conclusions

The overall efficacy and safety profile, and benefit/risk assessment, of nimesulide is favourable in comparison with other NSAIDs, including the coxibs.

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