NIMESULIDE
Better than the best
# Contents

**Introduction** ....................................... 2  
**Mechanism of Action**  ....................... 2  
**Clinical Profile of Nimesulide** ............ 3  

- **Nimesulide as Safe and Effective as Other NSAIDs** .......... 3  
  - ADRs associated with conventional NSAIDs .......... 4  
  - Nimesulide-induced ADRs ............ 4  

- **Nimesulide: A Step Above Others in Gastric Safety** .......... 4  
  - Tolerability of Nimesulide .......... 4  
  - Safety of Nimesulide ............ 6  
  - Nimesulide vs. conventional NSAIDs .......... 7  

- **Nimesulide: Benefit/risk Profile** ......... 9  
  - Overall View ............ 9  
  - Consensus report group on Nimesulide .......... 10  

**Conclusion** ..................................... 10  
**References** ..................................... 11
**Introduction**

Non-steroidal anti-inflammatory drugs (NSAIDs) play a fundamental role through wide spectrum of analgesic, anti-inflammatory and antipyretic activities. These drugs are as effective as analgesics in a variety of acute pain conditions. Globally, NSAIDs and cyclooxygenase-2 (COX-2) inhibitors (COXIBs) are most widely used medications. The use of NSAIDs plays a fundamental role in controlling inflammation and pain.

Nimesulide is a NSAID of the sulphonanilide class. It is different from conventional NSAIDs, which usually have a carboxyl or hydroxyl functional group. It was introduced in the Indian market in the early 1990s. Unlike other classical NSAIDs, it has high gastrotolerability due to its relatively high pKa value (6.5) and preferential COX-2 selectivity (COX-2/COX-1=0.19). This is perhaps one of the reasons (high efficacy and low gastric intolerance) that the drug is marketed in more than 50 countries, including India. There are more than 70 brands available in the Indian market. Nimesulide, a preferential COXIB is a non-carboxylic acid NSAID that has been effectively used for the treatment of a variety of inflammatory and painful conditions.

**Mechanism of Action**

Cyclooxygenase-1 (COX-1) is expressed in most tissues and is critical for the maintenance of normal platelet and renal function, and gastric mucosal integrity. On the other hand, COX-2 is expressed in inflammatory cells and is involved in the process of inflammation. The anti-inflammatory effects of NSAIDs depend mostly on inhibition of COX-2, whereas the gastrointestinal (GI) and renal side-effects depend on COX-1 inhibition. Nimesulide preferentially inhibits the enzyme COX-2 over COX-1 (Figure 1). Hence, nimesulide offers a good anti-inflammatory effect without major GI and renal toxicity. The other actions of nimesulide include:

- Prevention of cartilage damage by inhibition of metalloproteinase synthesis
- Inhibition of generation of superoxide anions from stimulated polymorphonuclear leucocytes
- Blocking of histamine release
- Prevention of bradykinin/cytokine-induced hyperalgesia of nerves (inhibiting release of TNF-α)
- Scavenging of hypochlorous acid
- Inhibition of phosphodiesterase type-IV
- Inhibition of the synthesis of platelet activating factor

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 conditions.
Clinical Profile of Nimesulide

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 from painful inflammatory symptoms, markedly superior to placebo and at least equivalent, or in some cases superior, to established NSAIDs (e.g., ibuprofen, naproxen, ketoprofen) and the newer class of highly selective COXIBs.4

It is mainly indicated for joint inflammation, osteoarthritic pain, fever, musculoskeletal conditions, acute pain including that from perioperative conditions, and dysmenorrhea. Nimesulide is also safe in aspirin-sensitive asthmatic patients. It is reported to be beneficial in relieving the symptoms of rhinitis, rhinopharyngitis, tubaritis and secretory otitis media with concomitant antibiotic treatment.5

Nimesulide as Safe and Effective as Other NSAIDs

NSAIDs differ in their tolerability profile, and this fact should be taken into account in the choice of drugs in relation to patient characteristics.6 Frequent use of NSAIDs are associated with severe or even serious adverse events, which increases the morbidity and mortality.7 The most common adverse drug reactions (ADRs) associated with NSAIDs, include GI disorder, renal disorder, hepatic disorder, asthma, allergic rash and disturbed hematopoiesis that results due to the inhibition of prostaglandin (PG) synthesis.8 Epidemiological evidence has also shown that NSAIDs may be associated

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Figure 1. Multi-model action of nimesulide

**NIMESULIDE**

**Preferential COX-2 inhibition**

- Inhibition of:
  - HIS, PAF, LTB4 release
  - Chemotaxis
  - Trans-endothelial migration
  - Elastase release
  - MMP release and activity
  - Monocyte death
  - Chondrocyte survival
  - NOS activity and NO production
  - ROS production

- Activation of:
  - Glucocorticoid receptors

**Major COX-2 Independent Activities**

- Inhibition of:
  - HIS, PAF, LTB4 release
  - Chemotaxis
  - Trans-endothelial migration
  - Elastase release
  - MMP release and activity
  - Monocyte death
  - Chondrocyte survival
  - NOS activity and NO production
  - ROS production

- Activation of:
  - Glucocorticoid receptors

**Analgesic Effect**

**Antipyretic Effect**

**COX-2 Inhibition (preferential)**

**Cytokine Inhibition**

HIS: Histamine; PAF: Platelet activating factor; LTB4: Leukotriene B4; MMP: Matrix metalloproteinase; NOS: Nitric oxide synthetase; NO: Nitric oxide; ROS: Reactive oxygen species
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with increased risk of cardiovascular (CV) events including congestive heart failure, increased hypertension and myocardial infarction.\textsuperscript{9-11}

**ADRs associated with conventional NSAIDs**

Pirmohamed and colleagues conducted a study to ascertain the current burden of ADRs through a prospective analysis of all admissions to hospital. In this study, it was observed that NSAIDs (such as aspirin, diclofenac, ibuprofen, rofecoxib, celecoxib, ketoprofen and naproxen) were the most common class of drugs responsible for causing ADRs (29.6\%).\textsuperscript{12} The typical ADRs of NSAIDs on various organs and systems are summarized in Table 1.

**Nimesulide-induced ADRs**

Clinically observed ADRs with nimesulide are similar to those associated with other NSAIDs (Table 1). However, nimesulide has a good overall tolerability irrespective of patient age, gender and tolerance of other NSAIDs.\textsuperscript{13} Spontaneous reporting of data has demonstrated that nimesulide is the most commonly prescribed analgesic associated with fewer GI disorders (such as GI perforation, bleeding and ulceration) when compared to other NSAIDs.

**Nimesulide: A Step Above Others in Gastric Safety**

Nimesulide is generally well tolerated in all patients including the elderly, who are often treated concomitantly with several medicaments and also children. Interaction with other drugs are uncommon and the incidence of ADRs in the elderly is comparable to that in young.\textsuperscript{14} The favorable efficacy and safety of nimesulide in different clinical situations, in pediatric as well as adult population have been demonstrated by its virtual presence on the prescription in more than 50 countries, both developed and developing, in the past 17 years.

**Tolerability of Nimesulide**

In a phase IV multi-center clinical study, conducted in 106 Swiss medical practices, 9.7\% of 2043 patients with various inflammatory and painful conditions receiving nimesulide experienced ADRs. The researchers concluded that the overall tolerability of nimesulide was very good/good in most of the cases (90.5\%).\textsuperscript{15} Results from an Italian post-marketing survey, which examined data from 22,938 patients with osteoarthritis treated with nimesulide therapy (1-3 weeks) demonstrated the good tolerability profile of nimesulide.\textsuperscript{16}

In a prospective, randomized double-blind study, nimesulide (100 mg bid) was associated with lower incidence of GI adverse effects (AEs) than ibuprofen

The weak acidity of nimesulide (pKa 6.5) and short plasma half-life contributes to its relatively good gastric tolerability due to an absence of oxidative phosphorylation uncoupling.
<table>
<thead>
<tr>
<th>Organ System</th>
<th>Conventional NSAIDs</th>
<th>Nimesulide</th>
</tr>
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<tbody>
<tr>
<td>Cardiovascular System</td>
<td>• NSAIDs can interfere with the antiplatelet activity of aspirin, worsen heart failure, increase blood pressure (BP), and increase the risk of CV disease. • In a meta-analysis, a total of 9,218 patients were evaluated to determine the risk of myocardial infarction (MI) due to NSAIDs. An increased risk of MI was evident in patients taking rofecoxib, diclofenac, and ibuprofen.</td>
<td>• Post-marketing data on nimesulide has shown that there have been relatively few CV ADRs (classified as both cardiac disorders and vascular disorders) reported to Helsinn healthcare from all the sources. • In an observational cohort study performed in Eire, a total of 3,807 patients received nimesulide. There were no reports of serious or non-serious adverse cardiac events.</td>
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<tr>
<td>Hepatic System</td>
<td>• NSAIDs exhibit a broad spectrum of liver damage ranging from asymptomatic, transient, hyper-transaminasemia to fulminant hepatic failure. • The incidence of liver disease induced by NSAIDs reported in clinical studies is fairly uniform ranging from 0.29/100000 [95% confidence interval (CI): 0.17-051] to 9/100 000 (95% CI: 6-15).</td>
<td>• Nimesulide hepatotoxicity shows a wide spectrum of liver damage including acute hepatitis, cholestasis, mixed forms, massive and submassive hepatic necrosis. The prevalence of rare and unpredictable hepatotoxicity with nimesulide is about 0.1 per 100,000 treated patients, which is similar to other NSAIDs like diclofenac. • Traversa and colleagues assessed the risk of acute hepatotoxicity associated with nimesulide in comparison to NSAIDs. This study demonstrated that the risk of liver injury in patients taking nimesulide and other NSAIDs is small.</td>
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<tr>
<td>Respiratory System</td>
<td>• Aspirin and other NSAIDs can induce severe and sometimes life-threatening bronchoconstriction in asthmatic patients. • Severe asthma and subsequent death following a single dose of rofecoxib has been reported.</td>
<td>• Nimesulide has been well-tolerated by most aspirin and/or NSAID-intolerant patients and in patients with asthma. • De Lucia et al., evaluated the effects of nimesulide (200 mg daily for 2 weeks) in comparison to placebo in patients with asthma. It was observed that nimesulide had no effect on airway hyper-responsiveness to either allergen or methacholine challenge.</td>
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<tr>
<td>Renal System</td>
<td>• NSAIDs can result in hemodynamically mediated failure (results from reduction in prostaglandin synthesis induced by the NSAID) and acute interstitial nephritis (results from a direct toxicity of the drug on the renal parenchyma). • Sites of low pH in the kidney may help explain the accumulation of NSAIDs and thus increases the potential for renal damage.</td>
<td>• As with other NSAIDs AEs in the renal system have been rarely observed with nimesulide (4.7%), which is relatively low in comparison with the standard NSAIDs. • It has a relatively short plasma half-life in humans that may attribute for its relatively few reports of renal toxicity. There is a small effect of COX-1 sparing in the kidney that might account for nimesulide being less likely to have nephrotoxic effects. Overall, the effects of nimesulide on hemodynamics and renal functions are similar to those observed with other NSAIDs.</td>
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<td>Skin</td>
<td>• NSAIDs are known to cause various adverse reaction on skin and are often reported to cause cutaneous reactions such as pruritus, morbilliform drug eruption, urticaria, pseudoporphyria, toxic epidermal necrosis (TEN), Steven Johnson Syndrome (SJS) and fixed drug eruption (FDE).</td>
<td>• Drugs with a short half-life, such as nimesulide, do not carry a higher risk for such cutaneous reactions. Nevertheless, nimesulide like other NSAIDs causes minor skin reactions (erythematous rashes, urticaria, etc.), and these are the most frequent of ADRs that have been reported.</td>
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<tr>
<td>Hematology</td>
<td>• Hematologic side–effects from NSAIDs are related primarily to their antiplatelet activity. One of the rare complications associated with NSAID therapy is development of neutropenia. • A case-control study demonstrated an increased risk of neutropenia with NSAID therapy. However, no particular risk factors were determined, and no specific NSAID was identified as being the main cause.</td>
<td>• Nimesulide has modest antiplatelet effects and short plasma half-life, which may account for nimesulide not being associated with serious hematological complications. • A randomized, double-blind, placebo-controlled study demonstrated that nimesulide 200 mg/day for 7 days neither prolonged bleeding time nor modified hemostatic variables.</td>
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<td>Gastrointestinal Tract</td>
<td>• NSAIDs cause peptic and duodenal ulcers, which may perforate and bleed and even lead to death. GI adverse effects are common and are observed in as many as 60% of individuals who use traditional NSAIDs per year. • NSAIDs may also injure the small intestine, leading to a spectrum of damage from a change in permeability through to inflammation and ulceration that may cause anemia and occasionally structure formation.</td>
<td>• The weak acidity of nimesulide (pKa 6.5) contributes to its relatively good gastric tolerability due to an absence of oxidative phosphorylation uncoupling. In addition, nimesulide’s relatively short plasma half-life could be a factor that contributes to its few reports of severe GI ADRs. • The members of the consensus report group on nimesulide demonstrated that the GI safety profile of nimesulide was better than other NSAIDs and placebo.</td>
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(600 mg tid). The results of spontaneous reporting from Italy demonstrated that GI AEs of NSAIDs such as diclofenac, ketoprofen, and piroxicam were found to be two-folds higher when compared to nimesulide.

Mauro Venegoni et al\textsuperscript{16} carried out a simulation on the expected number of hospitalizations for hepatopathies and upper GI bleedings (UGIBs) in Italy before and after the regulatory measures (2006 vs. 2009), taking into account the shifting of nimesulide prescriptions on other NSAIDs. This study, supports the finding that nimesulide may carry a lower-than-average risk of gastroduodenal toxicity in comparison with other NSAIDs (as reported in the Laporte’s study), which explains the greater number of UGIB events that were potentially associated with the shifting of the prescription from nimesulide to other NSAIDs in the simulation.

In the year 2007, a case-controlled study was done to investigate the gastroduodenal toxicity of NSAIDs in Finland. Among the six non-selective and semi-selective NSAIDs included in the analysis (ibuprofen, ketoprofen, naproxen, diclofenac, meloxicam and nimesulide), ibuprofen was the least gastrotoxic NSAID followed by nimesulide (with other NSAIDs showing higher odds ratios).

**Safety of Nimesulide**

Pharmacoepidemiological studies suggest that nimesulide is an effective NSAID with relatively favorable profile of safety. Further, the individual or inherent risk factors of the patient can predispose him/her to increased risk for development of nimesulide-associated unpredictable or idiosyncratic hepatic reactions. These include specific gene abnormalities, alteration in specific gene expression or epigenetic factors. The wide clinical efficacy with unique pharmacodynamic actions and beneficial gastrotolerability and bronchotolerability in comparison with other NSAIDs may outweigh the relative risk of nimesulide-associated liver reaction (common to the class NSAIDs) in the long-term use of the drug.

In an international survey (Brand Poll report) carried out on 300 doctors in Europe to assess the most recognized brands of anti-inflammatory drugs (product awareness), nimesulide not only ranked third in brand awareness, but it was also perceived as the most effective and one of the most safest drugs (perceived quality) in the NSAID market.\textsuperscript{20}

The review of the safety profile of nimesulide confirmed it to be, in general, similar to that of its class (Figure 2).\textsuperscript{30} 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 this drug.\textsuperscript{31,32} Demonstration of this favorable GI safety profile is also
Nimesulide: Better than the best

Evident from detailed molecular and cellular investigations that support the clinical profile. The combination of factors, including physicochemical properties (being a near neutral pKa compound in contrast to the conventional acidic NSAIDs), the sparing of COX-1, inhibition of GI protective PGs, 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.

A recent multicentre population-based case-control study, which is one of the largest on 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.

**Nimesulide vs. Conventional NSAIDs**

Clinically observed AEs with nimesulide have been typical of those found with other NSAIDs. There is a concern about the hepatotoxicity related to nimesulide. Most of the reported hepatotoxicity with the use of nimesulide has been in isolated case reports. The report of unexpected liver reaction to nimesulide may be viewed as a class phenomenon that occurs with all NSAIDs, including diclofenac, sulindac, etc. A few cases of hepatotoxicity have also been reported from India. However, in a post-marketing surveillance of nimesulide suspension (50 mg/ml) conducted through

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**Figure 2. Safety profile of nimesulide**

![Safety profile of nimesulide](chart)

Many reports and clinical study groups demonstrated that the GI safety profile of nimesulide was better than other NSAIDs and placebo.
600 pediatricians in India, no case of nimesulide-related hepatotoxicity was found. The strengths of this study were a large cohort of patients (4097 patients treated by 430 pediatricians) and conscious assessment of the drug under real-practice conditions as opposed to clinical trial conditions. An interesting observation noted in the above study was a failure of the development of any AEs in two patients with hepatitis who took nimesulide.

A post-marketing surveillance of nimesulide suspension (50 mg/ml), conducted through 600 pediatricians all over India, also indicates the absence of nimesulide-related hepatotoxicity in children. The incidence of rare and unpredictable liver reactions with nimesulide is about 0.1 per 100,000 treated patients, which is not higher than most of the other NSAIDs like diclofenac.

In a systematic review of published randomized controlled trials (involving 1254 subjects), no renal AEs were seen with the use of nimesulide. These data underscore the safety of nimesulide in patients with moderate renal failure.

In another double-blind, crossover study, short-term treatment with nimesulide (100 mg bid) produced less GI damage and reduced duodenum injury in terms of hemorrhagic lesions and erosive lesions when compared to naproxen (500 mg bid), (Figure 3). Wobber reported that a substantial double-blind multicenter study of acute shoulder found nimesulide to be at least as efficacious as diclofenac but with fewer side-effects. A meta-analysis of six trials in osteoarthritis shows that with short-term administration, nimesulide was at least as good as the other NSAIDs like diclofenac. Nimesulide has relatively low occurrences of GI ulcers and bleeding, asthma and respiratory tract reactions and does not appear to have the CV reactions [CHF, MI] that has been observed recently with the COXIBs and some other NSAIDs.
NSAIDs (diclofenac, etodolac, ketoprofen, naproxen, piroxicam) but had fewer side-effects particularly in relation to the GI tract.

**Nimesulide: Benefit/risk Profile**

**Overall View**

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. 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.31

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 CV AEs, are in line with that of the NSAID class. With particular reference to the CV safety profile of nimesulide, data from clinical trials and ADRs monitoring confirmed a low risk of CV events related to the use of the drug.

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.38

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 European Medicine Agency (EMEA) in 2003.39

This specific aspect was supported, among others, by the outcome from an independent epidemiological study, designed with the aim of evaluating the incidence of hepatic reactions due to use of NSAIDs in Italy.21 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. This slight increase in risk does not alter the overall good safety profile, especially if its GI safety profile is considered.29
Nimesulide: Better than the best

Consensus Report Group on Nimesulide

The Consensus Report Group on Nimesulide (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 dysmenorrhea. Nimesulide proved to be a valid therapeutic alternative to other NSAIDs, with a similar or even superior clinical efficacy, characterized by a fast onset of the analgesic action. Nimesulide shares the characteristic side-effects of NSAIDs, such as GI, skin, renal and hepatic reactions.

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 GI 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 ADRs over time or of any potentially ‘new’ ADRs or new signals related to nimesulide.

These statements together with the evidence from clinical studies, allows confirmation that the benefit/risk profile of nimesulide remains favorable and unchanged over time.

Conclusion

- According to 200 and more clinical trials conducted in more than 90,000 patients to evaluate the safety profile and efficacy of nimesulide, it has consistently shown relief from painful inflammatory symptoms, markedly superior to placebo and at least equivalent, or in some cases superior, to that of other established NSAIDs (e.g., ibuprofen, naproxen, ketoprofen) and the newer class of highly selective COXIBs.
- Available evidence suggests that nimesulide is an effective and well-tolerated NSAID alternative to other NSAIDs in the treatment of pain and inflammation due to various causes.
- In general, nimesulide exhibits the usual GI, dermatological and neurological adverse events associated with NSAIDs, of mild-to-moderate intensity.
- Clinical trials and large post-marketing surveillance studies has proved it to be well-tolerated by pediatric, adult and elderly patients.
- As the risks of respiratory tract allergies and intolerance in aspirin-intolerant asthma patients from nimesulide is very less, nimesulide can be given to patients with upper respiratory tract infections and ear, nose and throat (ENT) conditions with relative safety.
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 vs. other NSAIDs.

References

Nimesulide: Better than the best