# Nimesulide Induced Hepatotoxicity: Clinical Evidence, Case Studies, And Current Regulatory Status

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***Abstract*—Background Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) used to treat acute pain, fever, osteoarthritis, and menstrual cramps in adults. While it is highly effective often outperforming drugs like paracetamol or aspirin in reducing fever and inflammation its safety profile, specifically regarding the liver, remains a subject of intense medical debate. Findings Research indicates a complex "risk vs. benefit" scenario. Clinical Benefits: Nimesulide provides rapid analgesia and is generally well-tolerated by the gastrointestinal and renal systems compared to other NSAIDs. Hepatotoxicity Risks: Significant evidence suggests nimesulide increases the risk of liver injury. Meta-analyses show users are twice as likely to experience hepatotoxicity compared to non-users. In severe cases, this has led to fulminant hepatic failure, liver transplants, and death. Regulatory Status: Due to these risks, the drug has been banned in many countries (such as the US and Switzerland) and restricted in others. In India, while the pediatric use of nimesulide was banned in 2011, it remains available for adults despite ongoing concerns regarding its safety. While Nimesulide is a potent and effective anti-inflammatory, it carries a significantly higher risk of liver damage than other drugs in its class. Short-term use (less than 15 days) can still trigger adverse hepatic reactions. Therefore, while its efficacy is proven, its use requires strict medical supervision and a careful assessment of the patient's liver health.**

***Index Terms*—Nimesulide, NSAIDs, Cox-2 Inhibitors, Hepatotoxicity, Hepatic failure, Liver transplant, Acute pain, Osteoarthritis, Menstrual cramps, Drug ban, medical supervision, India (2011 ban).**

## I. INTRODUCTION

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) specifically designed to target the COX-2 enzyme. Since its debut in Italy in 1985, it has been marketed in over 50 countries across Europe, Asia, and Latin America under various brand names such as Aulin, Mesulid, and Nimed. It is widely used to treat acute pain, osteoarthritis, and menstrual cramps. Nimesulide is favored by many healthcare providers because it is highly effective. It is rapidly absorbed by the body, providing fast relief from pain and fever. Historically, it has been seen as a "safer" alternative to aspirin because it causes fewer stomach and gastrointestinal issues a common problem with older painkillers.

### 1.1. The Safety Concern: Hepatotoxicity:

Despite its effectiveness, Nimesulide is not available in the United States and has been withdrawn from several other markets (like Spain, Finland, and Ireland). The primary reason is hepatotoxicity, or drug-induced liver damage.

Key findings from clinical studies and regulatory reviews include:

Severe Liver Injury: While many side effects are mild, Nimesulide has been linked to rare but fatal cases of fulminant hepatic failure, sometimes requiring emergency liver transplants.

Co-existing Issues: In some patients, liver damage may occur alongside kidney (renal) impairment.
Regulatory Controversy: There is significant disagreement among global health authorities. While the European Medicines Agency (EMA) concluded in 2012 that the benefits outweigh the risks for certain uses, other countries have banned the drug entirely especially for children to prevent life-threatening liver complications.

1.2. Purpose of the Research:
Because Nimesulide is still widely used in many parts of the world, including India and South Korea, it is critical to evaluate its safety profile. This study aims to systematically review existing medical literature and meta-analysis data to determine the actual risk of liver injury compared to other common painkillers. By examining both clinical trials and real-world case reports, we aim to provide a clearer picture of how Nimesulide affects human health over short-term and long-term use.

## II. BACKGROUND AND HISTORY

Nimesulide was first approved in Italy in 1985 and is currently available in more than 50 countries.[1] It is a nonsteroidal anti-inflammatory drug (NSAID) and has been used globally as an effective treatment regimen for patients aged >12 years with fever, acute pain, acute tendinitis, osteoarthritis and dysmenorrhea.2 Nimesulide was first approved in India by the Drugs Controller General of India (DCGI) in 1995 in various dosages including nimesulide 100 mg tablet, nimesulide 50 mg/5 mL as suspension, nimesulide transdermal 1% gel for topical use and nimesulide 50 mg/100 mg as a suppository (rectal administration). In 1999, 200 mg dose of nimesulide was also introduced in the market as suppository. Fixed-drug combinations (FDCs) have been widely accepted as treatment options for a variety of diseases because of their superior therapeutic efficacy and safety, improved patient compliance and adherence and reduced cost to patients when compared with single-drug therapies. However, concerns have been raised regarding their irrationality and utility. FDCs have been gaining popularity in the Indian pharmaceutical market.4 Combinations of nimesulide with several other active drug compounds have been approved by DCGI.5 It was banned in 2000 in countries such as Switzerland, Spain and the US. As per an order dated 10th March 2011, nimesulide is not indicated for use in children below 12 years of age in India. Over 90,000 people have participated in more than 200 clinical trials examining the efficacy and safety profile of nimesulide in acute and chronic inflammatory and painful disorders, the results of which showed it to be significantly better than placebo and at least comparable or in a few cases superior to other active NSAIDs (ketoprofen, naproxen, ibuprofen) in the treatment of pain and inflammation. This paper aims to review the current scenario of nimesulide in adult patients and expert opinion

## III. MECHANISM OF ACTION

Nimesulide is a selective inhibitor of the cyclooxygenase (COX)-2 enzyme (Fig. 1). It has unique chemical and pharmacokinetic properties. Nimesulide imparts its pharmacological properties through a multifactorial mechanism of action (Fig. 2). It also inhibits phosphodiesterase IV and neutrophil function and renders antioxidant effects in human chondrocytes at a pharmacologic level; inhibits overexpression of tumor necrosis factor a (TNF-a) thereby regulating the release of other hyperalgesic cytokines. In an in- vivo study, nimesulide decreased interleukin (IL)-1B, IL-6 and TNF-a levels in a rat model of depression. In patients with knee osteoarthritis, nimesulide significantly reduced the level of pro-inflammatory cytokine IL-6.9

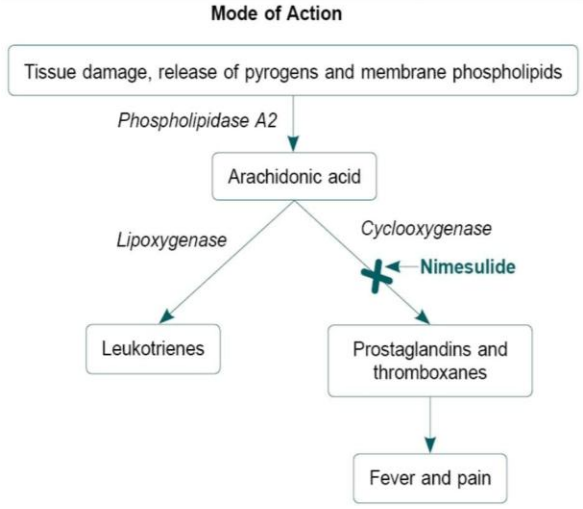

Figure No. 1 Mode of Action

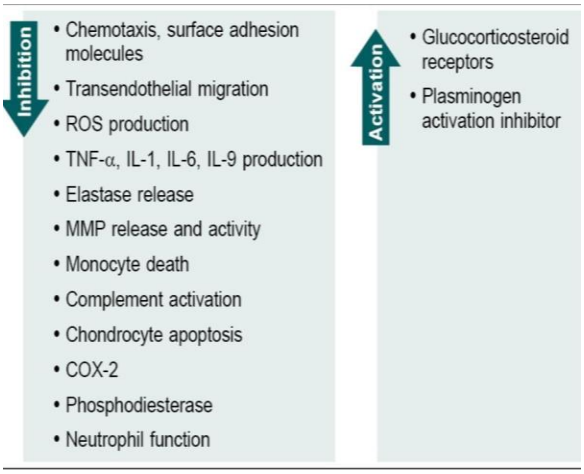


Figure No. 2 Mechanism of Action

## IV. CLINICAL EVIDENCE:

Nimesulide has been extensively studied for its role in managing fever, pain, and inflammation. Clinical evidence highlights its rapid onset of action and its comparative performance against other common medications.

### 4.1. Efficacy in Fever (Antipyretic Activity):

- Superior Speed:

Nimesulide often starts reducing fever within 15 minutes of administration, which is faster than paracetamol.

- Effectiveness:

Studies show it is highly effective in normalizing body temperature. In one Indian study, patients saw an average temperature drop from 103.2°F to 99.7°F.

- Comparison:

Clinical trials have found it superior or equal to paracetamol, diclofenac, and aspirin in terms of how quickly and effectively it reduces fever.

### 4.2. Efficacy in Pain Management (Analgesic Activity):

Nimesulide is noted for providing more rapid and effective pain relief during short-term use compared to several other NSAIDs:

- Osteoarthritis:

It has shown better pain relief and functional improvement than rofecoxib and celecoxib.

- Post-Surgical Pain:

It significantly reduces pain and complications following dental, ear, nose, throat, and knee surgeries.

- Acute Back Pain:

When compared to ibuprofen, nimesulide users reported a better capacity to perform daily tasks and improved physical mobility after 10 days of treatment.

- Dental Pain:

In comparative studies, a higher percentage of patients rated nimesulide's efficacy as "excellent" or "good" compared to ketoprofen.

### 4.3. Safety and Tolerability Profile:

While the risk of liver injury is a known concern (hepatotoxicity), clinical data also highlights several areas where nimesulide performs well:

- Gastrointestinal (GI) Health: Because it targets COX-2 more specifically than COX-1, it causes fewer stomach issues (like ulcers or bleeding) than drugs like ibuprofen, ketoprofen, or aspirin.
- Renal and Cardiovascular: Its impact on kidney function is generally temporary and similar to other NSAIDs. Serious heart-related events (like heart attacks), which have been a concern with other COX-2 inhibitors (coxibs), are rarely reported with nimesulide.
- Hepatic Stats: While severe reactions can occur, some large-scale clinical reviews involving over 64,000 patients reported no instances of liver failure, suggesting that significant injury may be linked to individual vulnerability (idiosyncratic reactions).

## V. PHARMACOLOGY OF NIMUSULIDE:

Nimesulide is a unique painkiller that belongs to the sulfonanilide class. Unlike traditional NSAIDs (like Aspirin), it is designed to be a "smart" drug that targets inflammation while sparing the stomach.

### 5.1 Selective COX-2 Inhibition:

The primary way Nimesulide works is by blocking an enzyme called COX-2.

- COX-2 is responsible for creating prostaglandins that cause pain and swelling at the site of an injury.
- COX-1 is a "good" enzyme that protects the stomach lining and kidneys. Nimesulide is highly

selective, meaning it focuses almost entirely on COX-2. Studies show it can be up to 2,512 times more selective for COX-2 than COX-1. This is why it generally causes fewer stomach ulcers compared to other painkillers.

5.2 Fast-Acting Relief:
Nimesulide is "lipophilic" (fat-loving), which allows it to be absorbed by the body very quickly. This results in a fast onset of action, often providing relief within 15 minutes of taking the drug.

5.3 "Beyond the Enzyme" Benefits:
Nimesulide does more than just block COX-2; it has several unique backup mechanisms:

- Protects Cartilage: It reduces the release of enzymes that eat away at joint cartilage, making it useful for osteoarthritis.
- Reduces Histamine: It helps limit the release of histamine, which is why some people who are allergic to other NSAIDs (and get asthma-like symptoms) can tolerate Nimesulide.
- Neutralizes Free Radicals: It stops white blood cells from releasing "superoxide anions"—toxic substances that can damage healthy tissue during inflammation.

## VI. BAN OF NIMUSULIDE:

Because of its link to severe liver toxicity (hepatotoxicity) including cases that resulted in liver transplants and death nimesulide has faced strict bans and restrictions worldwide.

6.1 Why was it banned?
While nimesulide is great at stopping pain, it can be unpredictable. In some patients, it causes rapid and severe liver failure. Because other, safer painkillers are available, many health authorities decided the risk was simply too high.

6.2 Global Regulatory Actions:
Many of the world's leading health organizations have pulled the drug from their markets:

- Complete Ban: Countries like the United States (FDA), Australia (TGA), and several European nations (such as Sweden, Finland, and Germany) do not allow the drug to be sold.
- Partial Ban (India): In 2011, the Indian government (CDSCO) banned nimesulide for pediatric use (children under 12). However, it is still legal for adults in India, often leading to it being sold over-the-counter without a prescription.

6.3 Banned "Cocktail" Medications:
In India, the Ministry of Health has specifically banned several Fixed-Dose Combinations (FDCs) where nimesulide was mixed with other drugs. These "cocktails" were found to be unsafe or irrational.
Common Banned Combinations Include:

- Nimesulide + Paracetamol
- Nimesulide + Diclofenac
- Nimesulide + Serratiopeptidase
- Nimesulide + Cetirizine + Caffeine
- Nimesulide + Tizanidine

6.4 The Problem with Over-the-Counter (OTC) Use:
A major concern raised by experts is that in countries where it is still available for adults (like India):

- Lack of Awareness: Many consumers buy it without knowing the liver risks.
- No Warning: Pharmacists often sell it as a common painkiller without warning patients about potential drug interactions or toxicities.
- Self-Medication: People often take it for minor issues, unaware that even short-term use (less than 15 days) can trigger a dangerous reaction in some individuals.

## VII. CASES REPORTED:

The following case reports highlight the real-world dangers of Nimesulide-induced liver damage across different ages and countries. These stories illustrate how the drug can cause everything from mild jaundice to fatal organ failure.

7.1. Pediatric Risk (India):
A 6-year-old boy was given Nimesulide for a fever without a doctor's prescription. Within four days, he developed jaundice (yellowing of the skin) and blood in his urine. Laboratory tests showed dangerously high liver enzymes. Fortunately, once the drug was stopped, his liver function returned to normal after nine days. This case highlights why the drug is now banned for children in India.

7.2. Adult Toxicity and Recovery (Saudi Arabia/Israel):

A 54-year-old woman taking Nimesulide for chronic back pain developed acute hepatitis, confirmed by a liver biopsy. Like the child in India, her liver began to recover within a month only after she stopped taking the medication. This shows that the damage is sometimes reversible if caught early.

7.3. Fatal Progression (United Kingdom):

A 58-year-old woman took Nimesulide for two weeks for back pain. Despite feeling sick after 10 days, she continued the drug. By the time she reached the hospital, she was confused and severely jaundiced. Her liver had suffered massive necrosis (cell death). She underwent an emergency liver transplant but died a day later from multi-organ failure.

7.4. Rapid Failure and Emergency Transplant (France):

In a terrifyingly fast case, a 49-year-old woman developed acute liver failure after taking Nimesulide for only 3 days. The toxicity was so severe it affected her brain function. She was saved only by an emergency liver transplant performed within 12 hours of her hospital admission.

7.5. Long-term Use and Anemia (Spain):

A 63-year-old woman used the drug for 7 months to treat joint pain. She developed a "clinical picture" of liver failure along with severe anemia that required multiple blood transfusions. She eventually required a liver transplant to survive.

7.6. Complications with Existing Illness (Brazil):

An 81-year-old woman took Nimesulide for just 6 days. She suffered from internal bleeding and collapsed. While she already had an underlying bile duct cancer, doctors concluded that Nimesulide likely triggered the final, fatal liver collapse.

## VIII. DIFFERENT NIMUSULIDE BRANDS IN INDIAN MARKET:

In India, Nimesulide is marketed under several popular brand names for adult use. Here are two of the most common:

8.1 NISE (by Dr. Reddy's Laboratories):

- Strength: 100mg Tablet.
- Primary Use: Treating inflammatory conditions like Rheumatoid arthritis, post-surgical pain, fever, and menstrual (period) pain.
- Advice: It should be taken with food to prevent stomach upset. It is recommended to use the smallest effective dose for the shortest time possible.

8.2 NIMREST (by Ranbaxy Laboratories):

- Strength: 100mg Tablet.
- Primary Use: Used as a "second-line" therapy (prescribed when other medicines haven't worked) for acute pain from osteoarthritis and menstruation. It also treats muscle sprains and strains.
- Restriction: Strictly not recommended for anyone under 12 years of age.

Availability of banned drugs in india:

## IX. THE RISKY REALITY: BANNED DRUGS IN INDIA:

History is full of medical tragedies (like Thalidomide) that warn us against the dangers of self-medication. Despite global warnings, several drugs that are banned or strictly limited in other countries are still easily available in India.

9.1 The Problem with Over-the-Counter (OTC) Sales:

In India, many powerful medications are sold without a prescription. This leads to serious health risks, including:

- Liver and Kidney Failure
- Heart Problems
- Severe Strokes and Skin Reactions

9.2 Nimesulide: A Special Concern:

- The Global Stance: Nimesulide was actually discovered in Switzerland, yet it was never even used there because of safety fears. The World Health Organization (WHO) has listed it as a "severely restricted" drug.
- The Indian Context: While the government banned its use for children in 2011, it remains a "top seller" for adults. Many people buy it as a simple painkiller, unaware that it can lead to liver transplants or death.

9.3 Other Dangerous Drugs Still in the Market:
Nimesulide isn't the only concern. Other drugs often found in Indian pharmacies include:

- Phenylpropanolamine (PPA): Often found in cough syrups; linked to a higher risk of strokes.
- Cisapride: Used for acidity but can cause dangerous heart rhythm abnormalities.
- Sibutramine: Used for weight loss but associated with heart attacks.
- Analgin: A painkiller banned in many countries for causing severe blood disorders.

9.4 Why This Matters:
Taking these drugs without a doctor's supervision is dangerous because of drug interactions (how medicines react with each other) and idiosyncratic reactions (unpredictable, severe side effects).

## X. RESULTS AND DISCUSSION:

The comprehensive review of clinical data, pharmacological properties, and real-world case reports regarding Nimesulide reveals a stark contrast between its therapeutic efficacy and its safety profile.

1. Therapeutic Efficacy vs. Risk:
Clinical evidence confirms that Nimesulide is a potent and fast-acting medication. Its COX-2 selectivity makes it superior to many traditional NSAIDs in terms of gastrointestinal tolerability and speed of onset (relief within 15 minutes). However, the "risk vs. benefit" ratio is skewed by its unpredictable hepatotoxicity. Meta-analysis indicates that users are twice as likely to suffer liver injury compared to non-users.

2. Severity of Adverse Events:
The case reports from India, the UK, France, and Brazil demonstrate that Nimesulide-induced liver injury is not always dose-dependent. Severe reactions, such as fulminant hepatic failure and massive hepatic necrosis, have occurred in as little as three days of use. While some patients recover upon drug withdrawal, others face fatal outcomes or require emergency liver transplants.

3. Regulatory Gaps in the Indian Market:
Despite being banned in major markets like the US and Australia, and restricted to adults in India since 2011, Nimesulide remains a top-selling drug in the Indian pharmaceutical sector. The prevalence of Fixed-Dose Combinations (FDCs) and the ease of Over-the-Counter (OTC) availability increase the likelihood of self-medication and accidental overdose, further escalating the public health risk.

## XI. CONCLUSION:

Nimesulide remains a medical paradox: it is an exceptionally effective anti-inflammatory and antipyretic, yet it carries a potential for life-threatening liver toxicity that exceeds most other drugs in its class Strict Supervision: Nimesulide should never be used as a first-line treatment or for minor ailments. It must only be used under strict medical supervision for short durations (less than 15 days). Public Awareness: There is an urgent need to educate consumers in India about the risks of OTC Nimesulide, specifically emphasizing that it is strictly prohibited for children under 12. Pharmacovigilance: Healthcare providers should prioritize monitoring liver enzymes (ALT/AST) in patients prescribed Nimesulide and immediately discontinue use at the first sign of nausea, jaundice, or dark urine. Ultimately, while the drug provides rapid relief, the availability of safer alternatives like Paracetamol or Ibuprofen suggests that the routine use of Nimesulide should be heavily discouraged to prevent avoidable fatalities.

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