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NARRATIVE REVIEW OF NIMESULIDE IN ADULTS: CURRENT SCENARIO

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ABSTRACT

Nimesulide, a nonsteroidal anti-inflammatory drug (NSAID) with preferential cyclooxygenase-2 (COX-2) inhibitory activity, has been extensively employed as an effective therapeutic agent in patients aged >12 years for the treatment of fever, acute pain, acute tendinitis, osteoarthritis, and dysmenorrhea. It has been reported to possess enhanced antipyretic and anti-inflammatory efficacy compared to paracetamol and aspirin, respectively, while providing analgesic effects comparable to other conventional NSAIDs.

Beyond its primary pharmacological actions, nimesulide exhibits additional properties such as modulation of inflammatory mediators, inhibition of free radical generation, and reduction of histamine release, which may contribute to its therapeutic effectiveness. The drug is characterized by a relatively rapid onset of action and favorable gastrointestinal tolerability when used within recommended dosage limits.

This review critically examines the current clinical status of nimesulide in adult populations, emphasizing available clinical evidence, safety considerations, and its use in special populations. Particular attention is given to its pharmacokinetic profile, mechanism of action, and comparative effectiveness against other NSAIDs, including selective COX-2 inhibitors (coxibs).

Although concerns regarding hepatotoxicity have been raised in certain cases, appropriate patient selection, dose regulation, and duration of therapy can significantly minimize associated risks.

Overall, in comparison with other NSAIDs, nimesulide demonstrates a promising balance of efficacy, safety, and tolerability, supporting a favorable benefit–risk ratio when used judiciously in clinical practice.

KEYWORDS: COX-2 inhibitor, fever, inflammation, NSAID, pain.

INTRODUCTION

Nimesulide is a widely used nonsteroidal anti-inflammatory drug (NSAID) belonging to the sulfonanilide class, recognized for its preferential inhibition of the cyclooxygenase-2 (COX-2) enzyme. Since its introduction into clinical practice, nimesulide has gained considerable attention due to its effective anti-inflammatory, analgesic, and antipyretic properties. Its unique pharmacological profile, characterized by selective COX-2 inhibition and additional non- prostaglandin-mediated actions, differentiates it from traditional NSAIDs.

Inflammation and pain are common clinical manifestations associated with a wide range of acute and chronic conditions, including musculoskeletal disorders, postoperative complications, and gynecological conditions such as dysmenorrhea. NSAIDs remain the cornerstone of therapy for these conditions; however, their use is often limited by gastrointestinal, renal, and cardiovascular adverse effects, primarily related to COX-1 inhibition. In this context, nimesulide offers a potential advantage due to its improved safety and tolerability profile.

In addition to its primary mechanism of action, nimesulide exerts multiple pharmacological effects, including inhibition of pro-inflammatory cytokines, reduction of oxidative stress, and modulation of inflammatory cell activity. These properties contribute to its rapid onset of action and effectiveness in alleviating pain and inflammation.

Despite its widespread use, nimesulide has been subject to regulatory scrutiny in certain countries due to concerns regarding hepatotoxicity. Nevertheless, when administered within recommended doses and duration, it has demonstrated a favorable benefit–risk profile in adult patients.

This review aims to provide a comprehensive overview of nimesulide, including its pharmacological properties, clinical efficacy, safety considerations, and current therapeutic applications in various disease conditions.

Background, History and Indications

Nimesulide was initially authorized in Italy in 1985 and is presently marketed in over 50 countries.[1] It is classified as a nonsteroidal anti-inflammatory drug (NSAID) and has been extensively utilized worldwide as an effective therapeutic agent for individuals aged >12 years in the management of fever, acute pain, acute tendinitis, osteoarthritis, and dysmenorrhea.[2] In India, nimesulide received its first approval from the Drugs Controller General of India (DCGI) in 1995 and has since been available in multiple dosage forms, including 100 mg tablets, 50 mg/5 mL oral suspension, 1% transdermal gel for topical application, and suppositories (50 mg/100 mg) for rectal administration. Subsequently, in 1999, a 200 mg suppository formulation was also introduced into the market.[3]

Fixed-dose combinations (FDCs) have been widely adopted as therapeutic alternatives for various diseases due to their enhanced clinical efficacy, improved safety profile, better patient compliance and adherence, as well as cost-effectiveness compared to monotherapy.
Nevertheless, their rationality and clinical relevance have been questioned in certain contexts. In India, FDCs have gained significant traction within the pharmaceutical sector.[4] Several combinations of nimesulide with other active pharmaceutical ingredients have been approved by the DCGI.[5] However, nimesulide has faced regulatory restrictions and was withdrawn or banned in certain countries, including Switzerland, Spain, and the United States, around the year 2000. Furthermore, according to a regulatory directive issued on 10th March 2011, its use is contraindicated in children below 12 years of age in India.

More than 90,000 subjects have been enrolled in over 200 clinical studies evaluating the efficacy and safety of nimesulide in both acute and chronic inflammatory and painful conditions. The findings from these studies indicate that nimesulide is significantly more effective than placebo and demonstrates efficacy comparable to, or in some cases exceeding, that of other NSAIDs such as ketoprofen, naproxen, and ibuprofen in alleviating pain and inflammation.

This article aims to provide a comprehensive overview of the current status of nimesulide in adult patients, with particular emphasis on clinical evidence, therapeutic applications, and expert perspectives.

Mechanism of Action

Nimesulide acts as a selective inhibitor of the cyclooxygenase-2 (COX-2) enzyme (Fig. 1)

and is characterized by distinctive chemical and pharmacokinetic attributes.[6] Its pharmacological effects are mediated through a multifaceted mechanism of action (Fig. 2).

In addition to COX-2 inhibition, nimesulide suppresses phosphodiesterase IV activity and modulates neutrophil function, while also exerting antioxidant effects in human chondrocytes at therapeutic concentrations. Furthermore, it inhibits the overexpression of tumor necrosis factor- alpha (TNF-α), thereby regulating the release of other pain-inducing (hyperalgesic) cytokines.[7]

Evidence from in vivo studies indicates that nimesulide significantly reduces the levels of pro- inflammatory mediators such as interleukin (IL)-1β, IL-6, and TNF-α in experimental rat models of depression.[8] In clinical settings, particularly among patients with knee osteoarthritis, nimesulide has been shown to markedly decrease the concentration of the pro-inflammatory cytokine IL-6.[9]

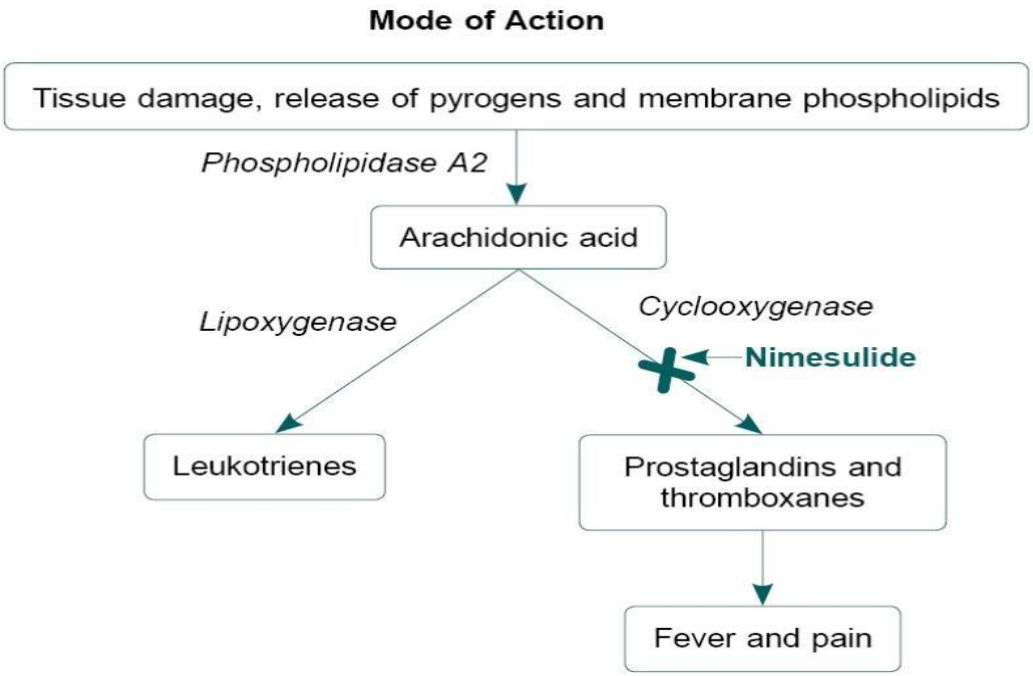

Figure 1. Mechanism of action of nimesulide.

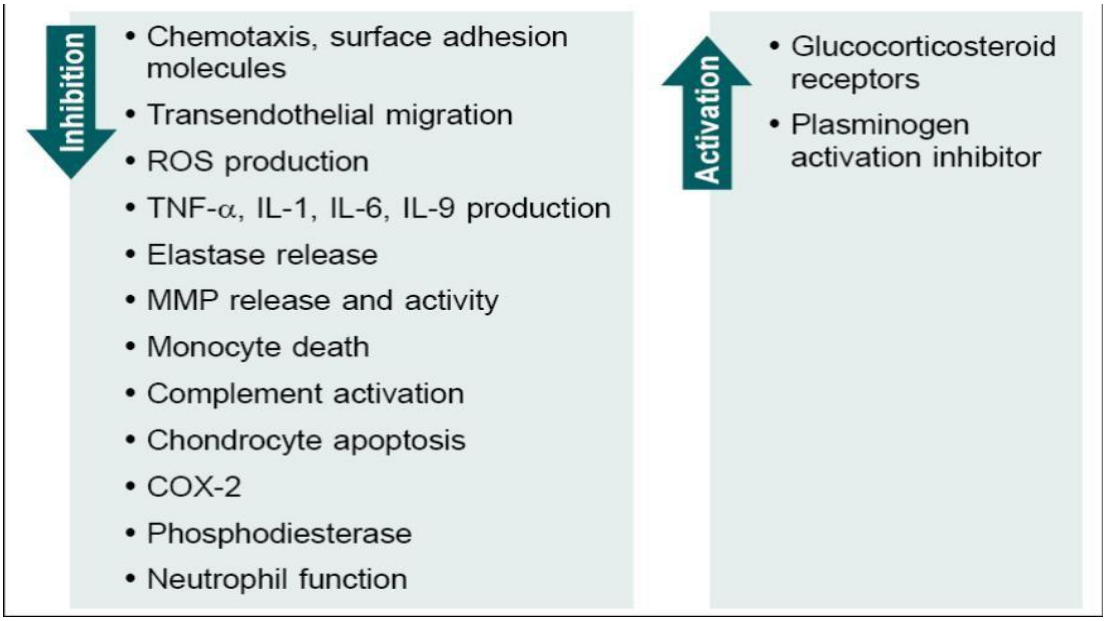

Figure 2. Multifactorial action of nimesulide.

ROS = Reactive oxygen species; TNF-a = Tumor necrosis factor a; IL = Interleukin; MMP = Matrix metalloproteinase; COX-2 = Cyclooxygenase-2.

Clinical Evidence

Nimesulide in Fever

Several clinical studies have assessed the antipyretic effectiveness of nimesulide in comparison with paracetamol, diclofenac, and acetylsalicylic acid. Nimesulide has been demonstrated to be superior to these agents in terms of efficacy, safety, and tolerability, with a rapid ability to reduce elevated body temperature.[2,10–12] It exhibits a quick onset of action, typically within 15 minutes of administration, compared with conventional antipyretics such as paracetamol.[2]

In a recent Indian study involving 302 adult patients with acute febrile illness, treatment with nimesulide resulted in a significant reduction in mean body temperature from 103.2 (±1.5)°F to 99.7 (±1.8)°F. Laboratory evaluations indicated no clinically significant changes in hepatic or renal parameters over a 14-day follow-up period, with only 2% of patients reporting mild adverse effects such as nausea and dyspepsia.[2]

Earlier investigations by Reiner et al. (1984, 1985) and Cunietti et al. (1993) demonstrated that rectal formulations of nimesulide (200 mg), diclofenac (100 mg), and paracetamol (500 mg) effectively reduced body temperature while normalizing heart rate and arterial pressure.

These treatments exhibited comparable efficacy and were generally well tolerated. Compared to placebo, nimesulide showed greater effectiveness in fever control and reduced the overall duration of febrile episodes, with only minor and transient adverse effects observed in treated groups.[10–12]

Nimesulide in Pain

Nimesulide is considered an effective, safe, and well-tolerated therapeutic option for the management of various inflammatory and painful conditions. In comparison with other NSAIDs such as etodolac, ibuprofen, naproxen, and rofecoxib, nimesulide demonstrates rapid onset and enhanced analgesic efficacy during short-term treatment.[6,13–20] Additionally, no significant increase in adverse events has been reported relative to other anti-inflammatory agents.

In randomized, double-blind comparative studies, nimesulide provided rapid pain relief and exhibited a favorable benefit–risk profile in patients with osteoarthritis of the knee, showing comparable or superior efficacy to placebo and other oral NSAIDs, including celecoxib and rofecoxib.[6,13]

Clinical investigations have also confirmed the effectiveness of nimesulide in managing postoperative pain and inflammation, including post-hemorrhoidectomy conditions, as well as after ear, nose, and throat (ENT), dental, oral, and arthroscopic knee surgeries.[21–25] Significant reductions in postoperative discomfort and complications have been reported with its use.

Comparative studies evaluating nimesulide against placebo and other analgesics such as ketoprofen, diclofenac (rectal), naproxen, and niflumic acid have consistently demonstrated its rapid and effective analgesic action.[21]

In a clinical trial conducted by Pierleoni et al., involving 46 patients undergoing dental surgery, nimesulide showed superior outcomes compared to ketoprofen. By the second postoperative day, night pain was absent in 69.5% of patients treated with nimesulide compared to 43.5% in the ketoprofen group. Furthermore, 91.3% of patients receiving nimesulide rated its efficacy as excellent or good, compared to 65.1% in the ketoprofen group, although improvements in sleep quality were similar in both groups.[23]

Binning et al. evaluated the efficacy of nimesulide (100 mg) compared with naproxen (500 mg) and placebo in 94 patients undergoing arthroscopic knee surgery. Nimesulide

significantly reduced mean pain intensity compared to both placebo and naproxen. Additionally, the median time required to achieve a 50% reduction in pain was shorter with nimesulide (0.82 hours) than with naproxen (1.05 hours) and placebo (1.33 hours), indicating a faster onset of analgesic effect.[25]

In patients with knee osteoarthritis, both nimesulide (300 mg) and rofecoxib (25 mg) demonstrated similar improvements in pain and quality of life. However, nimesulide showed superior outcomes in pain reduction and improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores after 30 days of treatment.[14]

Furthermore, in a comparative study assessing nimesulide and ibuprofen for acute low back pain, both drugs significantly improved pain and functional parameters. However, patients treated with nimesulide exhibited greater improvement in daily functional capacity and lateral spinal movement, along with a lower incidence of gastrointestinal adverse effects.[17]

Therapeutic Adjunct in COVID-19

Several in silico investigations have identified nimesulide as a potential candidate for the management of coronavirus disease 2019 (COVID-19).[26–28] Owing to its ability to interfere with the transport function of B0AT1, a receptor associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it may serve as an adjunctive agent in COVID-19 therapy.[29] Furthermore, selective inhibition of the COX-2 enzyme represents a plausible therapeutic strategy for mitigating pain and inflammation associated with viral infections.[30]

Certain NSAIDs have demonstrated anti-inflammatory effects in experimental models of influenza A infection, characterized by a reduction in pro-inflammatory cytokines such as TNF-α and IL-6, along with an increase in granulocyte colony-stimulating factor (G-CSF) levels in bronchoalveolar lavage fluid.[31] This experimental basis supported the consideration of nimesulide as a prophylactic or early-stage therapeutic option for mild COVID-19 symptoms in home settings, provided there is no history of hypersensitivity or toxicity.

The risk of hepatotoxicity associated with nimesulide is minimal when administered within the recommended dosage and duration. Clinical observations indicate that nimesulide is generally safe and well tolerated in the specified patient population, with only a small proportion of individuals reporting mild gastrointestinal discomfort.[32]

Safety Profile

Inhibition of the cyclooxygenase-1 (COX-1) enzyme is commonly associated with adverse effects such as gastrointestinal (GI) irritation, renal impairment, urinary disturbances, and cardiovascular complications. In vitro studies have demonstrated that nimesulide exhibits a higher selectivity for COX-2 inhibition compared to COX-1, which may contribute to its improved safety profile.[33]

Although GI-related symptoms such as dyspepsia and mild discomfort are among the most frequently reported side effects of NSAIDs, studies by Bjarnason et al. have indicated that nimesulide is comparatively better tolerated, with a lower incidence of serious complications such as intestinal perforation, ulceration, and GI bleeding.[34] Additionally, findings by Kress et al. and Famaey suggest that nimesulide is a preferred antipyretic agent with minimal clinically significant GI adverse events.[33,35]

Research by Laporte et al. has shown that the risk of upper GI bleeding associated with nimesulide is significantly lower than that observed with ibuprofen and markedly less than that reported with other NSAIDs such as ketorolac, ketoprofen, and piroxicam, which are known for poorer gastrointestinal tolerability.[36]

Hepatic adverse effects have been reported with several NSAIDs and are generally considered idiosyncratic reactions dependent on individual susceptibility. A systematic review by Sriuttha et al. highlighted clinically relevant hepatotoxicity associated with drugs such as diclofenac, celecoxib, and etoricoxib.[37] In contrast, nimesulide demonstrates a very low incidence of hepatic reactions (approximately 1–5 cases per 100,000 users), ranging from asymptomatic elevations in liver enzymes to rare instances of significant hepatic injury.[38,39] Notably, clinical studies involving approximately 64,000 patients treated with nimesulide reported no cases of hepatitis or liver failure.[34]

Both COX-1 and COX-2 enzymes play crucial roles in renal physiology, particularly in regulating the renin–angiotensin system and tubular electrolyte balance. Consequently, selective COX-2 inhibition by nimesulide may have a limited impact on renal function.[40,41] Nimesulide has been observed to exert transient effects on sodium and potassium excretion in healthy individuals. In clinical studies, administration of nimesulide (200 mg twice daily) attenuated increases in plasma renin and aldosterone induced by furosemide, while also reducing urinary prostaglandin E2 (PGE_2) excretion. Additionally, it increased urine output

and water excretion, while slightly decreasing glomerular filtration rate and renal plasma flow—effects that are consistent with those observed with other NSAIDs.[42,43]

Cardiovascular safety is another important consideration in NSAID therapy. Clinical evidence suggests that nimesulide is associated with a relatively low risk of cardiovascular events. Serious complications such as myocardial infarction and congestive heart failure, which have been reported with certain coxibs and other NSAIDs, are rarely observed with nimesulide.[34]

Expert Opinion

Nimesulide versus Nimesulide + Paracetamol Combination

Paracetamol is a widely used antipyretic and analgesic agent; however, it exhibits relatively weak anti-inflammatory activity. It acts as a non-selective inhibitor of the cyclooxygenase (COX) pathway, in contrast to nimesulide, which demonstrates preferential COX-2 inhibition.

With regard to analgesic efficacy and onset of action, the combination of nimesulide and paracetamol does not confer any additional pharmacological benefit over either agent used as monotherapy.[44] Both drugs exert their antipyretic and analgesic effects primarily through inhibition of prostaglandin (PG) synthesis, which plays a key role in mediating pain and inflammation.[45]

The use of irrational fixed-dose combinations may increase the likelihood of adverse effects. Although nimesulide has been reported to be a more effective and safer analgesic compared to several NSAIDs, its concomitant use with paracetamol is associated with an increased risk of hepatotoxicity. Therefore, it is essential to raise awareness among healthcare professionals and patients regarding the potential risks of such combinations and discourage their inappropriate use.[44]

Patient Profiles for Nimesulide

Arthritic Conditions

In patients experiencing moderate-to-severe pain associated with osteoarthritis of the hip and knee, nimesulide (100 mg twice daily) and diclofenac (50 mg three times daily) demonstrated comparable efficacy and overall tolerability. However, nimesulide was associated with a lower incidence of gastrointestinal adverse effects (36.3%) compared to diclofenac (47.2%), indicating a more favorable gastric safety profile.[46]

Nimesulide has also shown superiority over commonly prescribed NSAIDs such as celecoxib and rofecoxib in providing symptomatic relief in knee osteoarthritis. It exhibited a faster onset of analgesic action, particularly in pain associated with movement, compared to celecoxib, rofecoxib, and etodolac. Adverse event rates were low and comparable across treatment groups, suggesting that nimesulide offers equivalent or superior outcomes in terms of efficacy, tolerability, and quality of life.[13,14,16]

Dose-optimization studies involving 392 patients revealed that nimesulide produced rapid and sustained analgesic effects lasting up to 12 hours. Significant pain relief was observed within 1.5 hours at doses of 100 mg and 200 mg. While both 50 mg and 100 mg doses were well tolerated, the 200 mg dose showed a relatively higher incidence of adverse effects. Consequently, 100 mg administered twice daily has been identified as the optimal therapeutic dose for osteoarthritis management.[15]

These findings highlight that nimesulide is a distinctive NSAID with potent analgesic properties, making it highly effective in the management of arthritic disorders.

Dysmenorrhea

Nimesulide has demonstrated superior efficacy compared to other NSAIDs such as diclofenac, naproxen, and mefenamic acid, as well as placebo, in alleviating pain associated with primary dysmenorrhea.[47] It significantly reduces levels of prostaglandins, including PGF2α (which induces uterine contractions) and PGE_1/PGE_2 (which regulate uterine tone), by approximately 60% and 80%, respectively.[48,49]

Additionally, nimesulide facilitates the transition of uterine smooth muscle activity from abnormal dysmenorrheic contractions to normal physiological patterns and is associated with a reduction in uterine vascular resistance.[50,51]

In a multicenter, randomized, double-blind clinical trial involving 308 women, both nimesulide and diclofenac significantly reduced menstrual pain. However, nimesulide demonstrated a faster onset of action, with noticeable relief within 30 minutes and a greater reduction in abdominal discomfort. Both treatments were well tolerated, although gastrointestinal side effects were less frequent in the nimesulide group.[52]

Further studies indicate that nimesulide improves symptoms and reduces uterine artery impedance more rapidly than naproxen, without significantly affecting uterine or ovarian

blood flow in healthy women.[53] These findings support its clinical utility in managing primary dysmenorrhea.

Post-Surgical Pain

Nimesulide has shown comparable efficacy to naproxen and superior outcomes relative to placebo in reducing pain, inflammation, and edema following surgical procedures such as hemorrhoidectomy and arthroscopic knee surgery.[21,25] All treatments were generally well tolerated.

Comparative studies with ketoprofen in dental and third molar surgeries demonstrated that nimesulide provided superior pain relief, with faster recovery of functions such as mastication and swallowing. It was also effective in reducing postoperative edema and trismus.[23,54]

Additionally, studies involving rectal administration of nimesulide and diclofenac reported significant reductions in pain, swelling, hyperemia, and low-grade fever following procedures such as saphenectomy and inguinal hernioplasty, without notable adverse effects.[55] These findings support the use of nimesulide as an effective option for postoperative pain management with rapid onset of action.

Cancer Pain

Comparative studies evaluating nimesulide and naproxen in patients with advanced cancer pain have demonstrated comparable analgesic efficacy between the two agents. Nimesulide (200 mg twice daily) provided effective pain relief with a lower incidence of adverse effects, suggesting its potential role in the management of cancer-related pain.[19,20]

Ear, Nose, and Throat (ENT) Disorders

Multiple multicenter clinical trials have assessed the efficacy and tolerability of nimesulide in comparison with other anti-inflammatory agents such as seaprose-S and ketoprofen in ENT disorders.[22,56,57] Nimesulide effectively reduced inflammatory symptoms and demonstrated a faster onset of action. Although all treatment options were generally well tolerated, nimesulide showed consistent effectiveness in reducing swelling and hyperemia associated with postoperative ENT conditions.

Airway Inflammation

Nimesulide has demonstrated beneficial effects in modulating inflammatory responses in respiratory conditions such as rhinopharyngitis, rhinosinusitis, tubaritis, rhinitis, and middle

ear disorders. When combined with mucolytic agents such as ambroxol, it exhibits comparable anti- inflammatory activity.[58]

Oral administration of nimesulide has also been shown to be effective and well tolerated in patients with aspirin-sensitive asthma.[59] In individuals with chronic mucus hypersecretion, treatment with nimesulide for three weeks significantly reduced sputum viscosity without causing serious adverse effects.[60]

CONCLUSION

Nimesulide is a newer-generation nonsteroidal anti-inflammatory drug (NSAID) characterized by a distinctive chemical structure and preferential inhibition of the cyclooxygenase-2 (COX-2) enzyme, with relatively minimal activity against COX-1. This selective action contributes to its broad therapeutic applicability as an anti-inflammatory agent through a multifactorial mechanism.

Nimesulide exhibits a rapid onset of analgesic action in the management of pain and inflammation, mediated through both central and peripheral pathways. Clinical evidence supports its efficacy, safety, and tolerability in the treatment of various acute painful conditions, including postoperative pain, soft tissue inflammation, odontostomatological pain, extra-articular trauma, osteoarthritis, and cancer-related pain.

The incidence of hepatic adverse effects associated with nimesulide is comparable to that observed with other conventional NSAIDs and selective COX-2 inhibitors (coxibs). Overall, nimesulide demonstrates a favorable balance between efficacy, safety, and tolerability when compared to other NSAIDs, resulting in an acceptable benefit–risk profile.

Furthermore, as an antipyretic agent, nimesulide is effective and relatively safe in the management of fever when administered for short durations and within recommended dosage limits.

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