International Journal of Community Medicine and Public Health
*Manderwad GP et al. Int J Community Med Public Health. 2026 Aug;13(8):4748-4752*
https://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040
DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20262769

**Review Article**

# Nafithromycin: a pharmacological and microbiological overview of a new-generation lactone-ketolide for combating antimicrobial resistance

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**Received:** 06 June 2026
**Accepted:** 14 July 2026

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## ABSTRACT

There has been a rapid increase in antimicrobial resistance, particularly among respiratory pathogens, which poses a serious global challenge to the effective treatment of infectious diseases. Nafithromycin is a next-generation macrolide antibiotic and India's first indigenously developed drug in this class, representing a major therapeutic breakthrough after more than three decades. Based on its chemical structure, nafithromycin is categorized as a lactone-ketolide. This agent demonstrates favorable pharmacokinetic and pharmacodynamic properties along with enhanced hepatic safety when compared to earlier ketolides. Nafithromycin also exhibits improved ribosomal binding and excellent lung tissue penetration. This review focuses on the pharmacological and microbiological aspects of nafithromycin, including its antimicrobial spectrum, safety profile, clinical trial data, and overall tolerability.

**Keywords:** Nafithromycin, Community acquired pneumonia, Antimicrobial resistance, Macrolide

## INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the most serious global public health threats, significantly affecting the management of respiratory tract infections. Community-acquired respiratory pathogens, particularly Streptococcus pneumoniae, have shown increasing resistance to commonly used antibiotics such as macrolides, β-lactams, and fluoroquinolones, thereby limiting therapeutic options and increasing treatment failure rates.[1] The widespread and often inappropriate use of antibiotics has accelerated the emergence of multidrug-resistant (MDR) strains, leading to prolonged hospital stays, increased healthcare costs, and higher mortality rates.[2] According to the World Health Organization, AMR is projected to become a leading cause of death worldwide if effective antimicrobial stewardship and novel antibiotic development strategies are not implemented.[3] Macrolide antibiotics have played an important role in the treatment of respiratory tract infections for many years, however, their clinical effectiveness has declined due to the development of bacterial resistance mechanisms such as ribosomal methylation and efflux pump expression.[4,5]

### *Emergence of ketolides as advanced macrolide derivatives*

Erythromycin, the first clinically significant macrolide introduced in the 1950s, demonstrated effective activity against Gram-positive cocci and atypical respiratory pathogens.[6] However, the clinical utility of early macrolides was limited by poor acid stability, gastrointestinal intolerance, and the rapid emergence of bacterial resistance.[6,7] To overcome these limitations, newer macrolides such as azithromycin and clarithromycin were developed with improved pharmacokinetic properties and enhanced antimicrobial activity.[6] Despite these advancements, increasing resistance mediated primarily through erm-mediated

ribosomal methylation and mef-associated efflux mechanisms significantly reduced its effectiveness of conventional macrolides against respiratory pathogens.[7,8] This growing antimicrobial resistance prompted the development of ketolides, a semisynthetic derivative of macrolides designed to possess stronger ribosomal binding affinity with improved activity against macrolide-resistant strains.[9] Telithromycin became the first ketolide introduced into clinical practice. Telithromycin was engineered to overcome the macrolide resistance, but it has been found to be associated with severe hepatotoxicity and severe visual disturbances. Organisms developed resistance towards telithromycin through development of dual ribosomal mutations and high level ribosomal methylation due to the expression of erm dimethyltransferases.[9,10] A new drug nafithromycin, has demonstrated promising efficacy and safety in community-acquired bacterial pneumonia (CABP) to overcome the telithromycin resistance.[9,10] A detail comparison and differences in pharmacological and clinical properties of telithromycin and nafithromycin has been enlisted in Table 1.

**Table 1: Comparison of pharmacological and clinical properties of ketolide antibiotics.[11-16]**

| Parameters | Telithromycin | Nafithromycin |
|---|---|---|
| **Generation/class** | First approved ketolide | Novel lactone ketolide |
| **Approval Status** | Approved in some countries; restricted use | Approved in India for CABP |
| **Main indication** | Community-acquired respiratory infections | Community-acquired bacterial pneumonia (CABP) |
| **Mechanism of action** | Binds 50S ribosomal subunit and inhibits protein synthesis | Strong dual binding to 23S rRNA domains II and V |
| **Activity against macrolide-resistant strains** | Moderate | Excellent |
| **Major organisms covered** | S. pneumoniae, H. influenzae, atypicals | MDR S. pneumoniae, atypicals, respiratory pathogens |
| **Lung penetration** | High | Very high intrapulmonary penetration |
| **CYP interaction** | Strong CYP3A4 | Lower interaction potential |

## NAFITHROMYCIN

Nafithromycin is a novel ketolide antibiotic with potent activity against multidrug-resistant respiratory pathogens, particularly macrolide-resistant *Streptococcus pneumoniae*.[17] Owing to its enhanced ribosomal binding and improved intracellular penetration, nafithromycin has emerged as a promising therapeutic option in the era of increasing antimicrobial resistance.[18] The drug received DCGI approval in India and has also gained recognition under ICMR-supported antimicrobial resistance initiatives, highlighting its clinical significance in respiratory tract infections.[19]

### *Pharmacological profile of nafithromycin*

*Clinical trial and pharmacokinetic data*

Phase I clinical studies have demonstrated that nafithromycin has good and rapid oral absorption, with dose-dependent increases in plasma concentration and area under the curve (AUC).[20] Food intake exhibited slight increase in bioavailability. Steady-state plasma concentrations are achieved within 3-4 days, supporting its short-course dosing strategy.[20]

The efficacy related to antibacterial activity of nafithromycin correlates with the AUC/MIC ratio, which is the main PK-PD index governing macrolide activity.[1] High lung tissue penetration and concentrations relative to plasma levels allow sustained antimicrobial exposure at the site of infection, showing its effective three-day treatment regimen.[20,21]

Nafithromycin undergoes moderate CYP3A-mediated metabolism but shows weak inhibition of CYP3A and no inhibition of CYP2D6, minimizing the potential for clinically significant drug–drug interactions.[22] Its hydrophilic nature allows partial renal elimination of unchanged drug, thereby reducing hepatic burden.

Nafithromycin represents the first globally developed antibiotic in its class in more than 30 years, underscoring the success of rational drug design and public-private collaboration in antimicrobial innovation. As an indigenously developed pharmaceutical innovation, it strengthens national and global efforts to combat antimicrobial resistance and provides a model for future antibiotic development programs.[22]

Nafithromycin acts by binding to 50S ribosomal subunit and inhibits bacterial protein synthesis. Unlike conventional macrolides that bind primarily to domain V of the 23S rRNA, nafithromycin exhibits dual binding to both domains II and V, optimizing ribosomal affinity and maintaining antimicrobial activity against macrolide-resistant strains.[23] This dual-site binding stabilizes the ribosome-drug complex and prevents peptide chain

elongation even in the presence of resistance-associated mutations.

In a phase III randomized controlled trial involving 488 CABP patients, oral nafithromycin demonstrated non-inferior efficacy compared with moxifloxacin. The early clinical response rate in the MITT population was 91.3% with nafithromycin versus 89.0% with moxifloxacin. Notably, nafithromycin achieved comparable efficacy with a shorter 3-day treatment regimen. Adverse events such as diarrhoea, abdominal pain, headache, and nausea were generally mild.[24]

### *Antimicrobial spectrum*

Nafithromycin demonstrates robust in vitro activity against a broad range of respiratory pathogens, including macrolide-resistant *S. pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[24] In addition, nafithromycin exhibits remarkable activity against atypical and intracellular pathogens such as *Chlamydia pneumoniae*, attributable to its high intracellular accumulation.[24]

### *Strategies to counteract resistance*

By targeting conserved regions of the ribosome and avoiding exclusive dependence on a single binding site, nafithromycin effectively circumvents common macrolide resistance mechanisms, including erm-mediated ribosomal methylation and mef-mediated efflux pumps. This property is specifically significant in regions with high prevalence of macrolide-resistant organisms.[25]

### *Safety*

Preclinical safety studies conducted in rats and dogs demonstrated that nafithromycin did not produce any adverse hematological, biochemical, or histopathological changes, even at exposures several-fold higher than the intended therapeutic levels, indicating a favorable safety profile.[26] This contrasts with earlier ketolides, which have been associated with hepatotoxicity Although reversible phospholipidosis was observed in certain non-hepatic tissues, it was not associated with any functional organ impairment.[27]

### *Efficacy*

Clinical pharmacology and microbiological data support the use of nafithromycin in the treatment of community-acquired bacterial pneumonia (CABP), demonstrating excellent tolerability and efficacy comparable to standard fluoroquinolone therapy.[27,28] Nafithromycin works well against bacteria that are resistant to other antibiotics and also against atypical pathogens.[29] Its short and convenient dosing regimen improves patient compliance and may help limit the development of further antimicrobial resistance.[27,28]

### *Future perspectives and clinical implications*

The emergence of multidrug-resistant respiratory pathogens has emphasized the urgent need for newer antimicrobial agents with improved efficacy and safety profiles. Nafithromycin represents a promising addition to antimicrobial stewardship strategies because its short-duration therapy may help reduce unnecessary antibiotic exposure and improve patient adherence.[30] The availability of an effective 3-day oral regimen could also decrease selective antibiotic pressure and potentially limit the further development of antimicrobial resistance.

As India faces a substantial burden of community-acquired respiratory infections and increasing macrolide resistance among pneumococcal isolates, nafithromycin may play an important role in optimizing outpatient management of community-acquired bacterial pneumonia (CABP).[31] Being the first indigenously developed ketolide antibiotic from India, nafithromycin additionally highlights the growing capability of the Indian pharmaceutical sector in innovative antimicrobial drug development.[30]

The potent activity of nafithromycin against macrolide-resistant and atypical respiratory pathogens suggests potential future utility in difficult-to-treat respiratory infections and infections caused by multidrug-resistant organisms.[32] Its favorable pulmonary penetration and reduced drug-drug interaction potential further support broader clinical applicability, particularly in elderly patients and individuals with multiple comorbidities.

Despite encouraging clinical trial data, continued post-marketing surveillance and real-world pharmacovigilance studies remain essential to monitor long-term safety, emerging resistance patterns, and rare adverse effects. Ongoing surveillance will be critical to preserve the clinical utility of nafithromycin and ensure its appropriate integration into antimicrobial stewardship programs.[33]

## CONCLUSION

Nafithromycin shows good oral absorption and a favorable safety profile. Its ability to bind to two ribosomal sites, broad antimicrobial activity, beneficial pharmacokinetic–pharmacodynamic profile, and good tolerability make it different from older macrolides and ketolides. In the present era of increasing antimicrobial resistance, nafithromycin provides a promising and much-needed treatment option for resistant respiratory infections.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Manderwad GP, Venepally S, RajKumar HRV, Tipparti SK, Pavani ANT. Nafithromycin: a pharmacological and microbiological overview of a new-generation lactone-ketolide for combating antimicrobial resistance. Int J Community Med Public Health 2026;13:4748-52.