

# A prescription event monitoring study on the utility of garenoxacin, a newer fluoroquinolone in India

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## ABSTRACT

**Background:** Prescription event monitoring (PEM) study is conducted worldwide. The main objective of such study is to monitor the adverse events when a drug is being prescribed in “real life clinical” settings. PEM studies are being looked upon as an essential observational tool of postmarketing surveillance. Garenoxacin, a newer fluoroquinolone offers an excellent spectrum of antimicrobial coverage, which includes Gram-positive, Gram-negative, anaerobes and atypical microorganism. This broad spectrum of activity is attributed to its unique structure. **Aim:** The aim was to assess the safety profile of garenoxacin in Indian settings. **Materials and Methods:** A total of 400 doctors across the country participated in the study. Data from 12,498 patients was obtained. Monitoring of each patient was done for any adverse events. **Results:** As an initial line of therapy garenoxacin was preferred in majority of cases of community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis. Adverse events were reported in 159 patients which included 0.5% cases with nausea/vomiting, 0.1% cases with diarrhea. Central nervous system side-effects like drowsiness or dizziness was reported in 0.02% of the cases. All the adverse events were of mild to moderate severity and did not require hospitalization. **Conclusion:** Garenoxacin a novel desfluoroquinolone appears to be an ideal antimicrobial agent for the treatment of various respiratory tract infections including CAP. With superior safety profile, excellent antimicrobial coverage and a convenient once a day dosing garenoxacin appears to improve the patient compliance.

**Key words:** Adverse events, garenoxacin, prescription event monitoring, respiratory tract infections, safety

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## INTRODUCTION

Community-acquired respiratory tract infections (RTIs) represent one of the most common and important infections that are treated by clinicians.<sup>[1]</sup> It is becoming increasingly difficult to treat RTIs and otorhinolaryngological infections owing to the increase in resistant Gram-positive and Gram-negative bacteria.<sup>[2-4]</sup>

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Depending on local prevalence, empirical antibacterial therapy is often directed against *Streptococcus pneumoniae* (including penicillin resistant *S. pneumoniae* [PRSP]), *Haemophilus influenzae*, *Moraxella catarrhalis*, methicillin-susceptible *Streptococcus aureus*, “atypical pathogens” (*Mycoplasma*, chlamydia and *Legionella* spp.) and under appropriate clinical settings, Gram-negative bacilli and anaerobes.

Garenoxacin with a broad spectrum of coverage appears to be an ideal agent in the treatment of such infections.<sup>[5]</sup>

## MATERIALS AND METHODS

A prescription event monitoring (PEM) study was conducted between July 15, 2013 and September 15, 2013 with 400 doctors across India. A PEM study booklet, containing a letter of introduction to the doctor, a PEM report form, and a study flow chart with a patient log sheet, was sent to these prescribing doctors, requesting information on any “events” that occurred during the observation period of the prescription. From each doctor, observations from

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his/her patients were requested for whom garenoxacin 400 mg (200 mg, 2 tablets stat once a day) was prescribed for 5–14 days depending upon the severity of the infection and as per the details of the prescribing information sheet provided.

The term “events,” in PEM study, is defined as, including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in their chest disease or a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint that was considered of sufficient importance. The PEM report form also included additional questions like the indication for which garenoxacin was prescribed, duration of treatment, concurrent medical history (whether the patient had a history of diabetes mellitus, HIV and tuberculosis) and the final outcome of the disease. During the observation period, each patient was observed for any “events” that may arise thereof that noted in PEM report form and notified immediately to sponsor pharmacovigilance center in case of serious adverse events including death, disability, hospitalization or congenital anomaly. At the end of the observation period, the PEM booklets were collected. Based on the safety profile or observations with the drug, additional follow-up was done with the prescribing doctors for confirmation and causality assessment based on the pharmacological properties, concurrent disease or drug use.

Descriptive statistics was used to present the data.

## RESULTS

### Baseline demographics

Data from 12,498 patients was available at the end of the observation period. Amongst the patients who were prescribed garenoxacin, 70.3% patients were males and 29.7% patients were females with a mean age of 47.9 years. Patients were initiated on garenoxacin therapy for various community-acquired infections based on the clinical suspicion of bacterial etiology especially in terms of presenting symptoms with or without the associated laboratory findings or concomitant risk factors and/or medical history [Figure 1].

The baseline demographic parameters of the study representing gender, age, medical history and antibiotic use amongst the patients are shown in Table 1.

Garenoxacin was clinically evaluated for its utility in community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), upper RTI (pharyngitis/tonsillitis), sinusitis, skin and skin structure infections (SSSTIs), and urinary tract infection (UTI) as shown in Figure 2.

Garenoxacin was prescribed at a dose of 400 mg OD (200 mg × 2 tablets) with the duration varying from 5 to

**Table 1: Baseline demographic parameters of the study**

Study details	Number of patients	Percentage of patients
Total number of patients: 12,498		
Mean age: 47.9 years		
Gender		
Males	8786	70.3
Females	3712	29.7
Medical history		
Diabetes	2381	19.1
Tuberculosis	597	4.8
HIV	40	0.3
Prior use of antibiotics		
Levofloxacin	206	1.7
Amoxicillin-clavulanate	187	1.5
Moxifloxacin	79	0.6
Cefpodoxime	31	0.3
Cefixime	29	0.2
Azithromycin	29	0.2
Personal history		
Smokers	3,744	30

14 days depending upon the severity of condition, especially for lower RTIs (LRTIs), including CAP. Garenoxacin was preferred as first-line therapy among patients with CAP (84.6%) or AECB (85.2%) usually for 5–7 days [Figures 3 and 4].

In these cases of LRTIs, garenoxacin was usually prescribed for 5–7 days. Amongst the 3921 patients with AECB, garenoxacin was prescribed for 77.3% patients for 5 days, 19.9% patients for 7 days and 2.7% patients for 14 days.

### Clinical assessment

Clinical response was judged by subjective assessment for control of presenting symptoms. Data records were available for 11,698 patients with 8303 (70.9%), 3322 (20.4%) demonstrating cure and improvement rate respectively. Two failure cases were noted during the course of the observation period that was managed symptomatically in the outpatient setting without further hospitalization. Cure, improvement and failure was suggested by the treating physician as:

#### Cure

Complete disappearance of clinical signs and symptoms within the treatment period.

#### Improvement

Subsidence of clinical signs and symptoms (50%) but with incomplete resolution.

#### Failure

Unchanged or worsening of baseline clinical signs and symptoms.

### Event analyses

159 patients reported adverse drug reactions that were

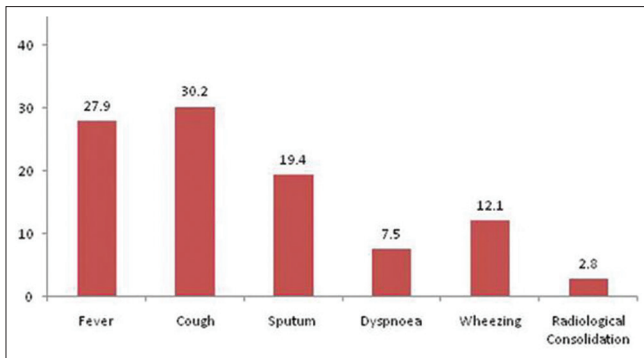


Figure 1: Symptom distribution of patients on garenoxacin

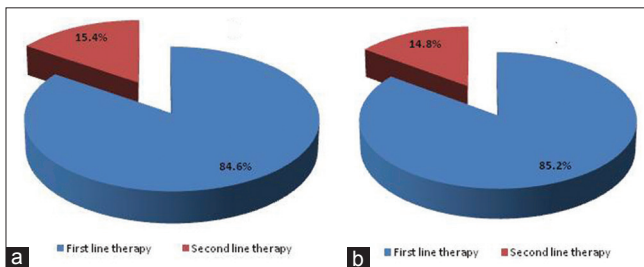


Figure 3: Choice of garenoxacin therapy in (a) community-acquired pneumonia and (b) acute exacerbations of chronic bronchitis

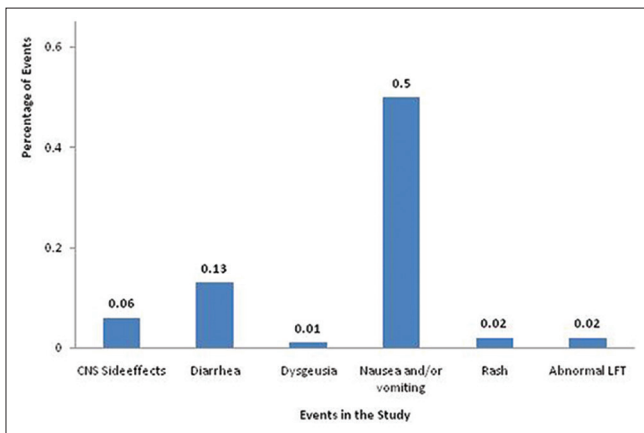


Figure 5: Analyses of “events” with the use of garenoxacin at the end of the study

mainly mild and transient. The side effects noted were mainly gastrointestinal disturbances in form of diarrhea, nausea and/or vomiting and dysgeusia [Figure 5].

## DISCUSSION

Community-acquired pneumonia appears to be a global concern with a significant morbidity and mortality. In Europe, it affects approximately 1.6–10.6/1,000 adult populations every year.<sup>[6]</sup> Guidelines commonly adopted by the physicians for the treatment of CAP are the Infectious Disease Society of America (IDSA)/American Thoracic Society. The current IDSA guidelines of 2012<sup>[7]</sup> suggests the use of respiratory fluorquinolones such as moxifloxacin, gemifloxacin, and

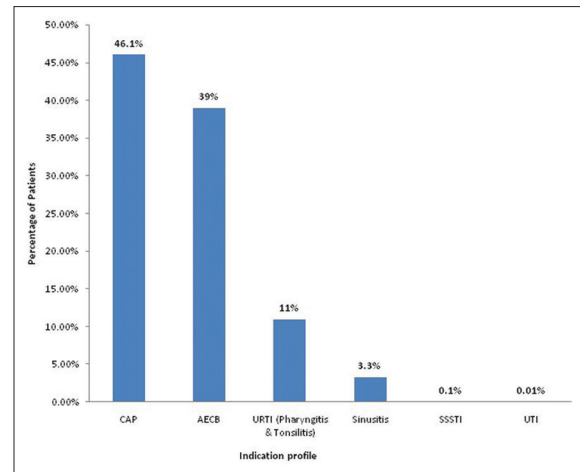


Figure 2: Clinical utility of garenoxacin in the study

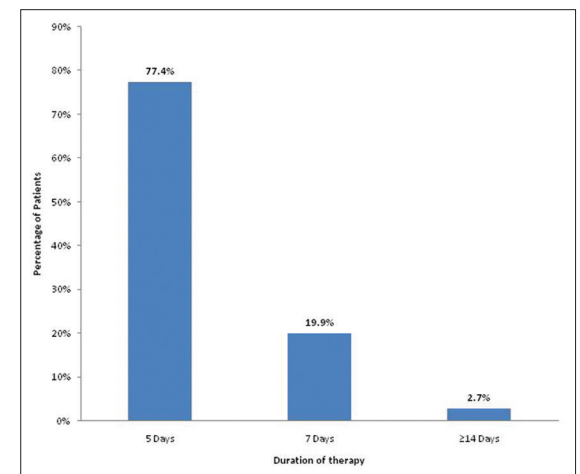


Figure 4: Duration of therapy in patients with acute exacerbations of chronic bronchitis on garenoxacin

levofloxacin in the treatment of CAP. The aim of the therapy should be to use antibiotics, which can target common pathogens at lower minimum inhibitory concentrations (MIC<sub>90</sub>).

Surveillance studies conducted worldwide have shown rising MICs for amoxicillin – clavulanate combinations with ≈ 4–7% strains demonstrating MICs of 4 mg/L.<sup>[8,9]</sup> These strains are not covered with classical dosage administration of 625 mg for the combination given 3 times a day and require further higher dose supplementation.<sup>[6]</sup> Ho et al.,<sup>[10]</sup> demonstrated fluoroquinolone resistance emerging in South East Asian countries including Hong Kong where the resistance rates have been 13.3% and 8.9% for levofloxacin and moxifloxacin respectively. Similarly in Asian population, the high prevalence of atypical pathogens (23.5%) amongst CAP patients presents a unique challenge in empirical management.<sup>[11]</sup> However the high rates of macrolide-resistant *Mycoplasma pneumoniae* reported in China (>90%) and Japan (87.1%)<sup>[12,13]</sup> have only increased

our efforts in quest for a safe yet effective antibiotic against community-acquired infections.

### *Streptococcus pneumonia*

Worldwide there has been a steady rise in the prevalence of PRSP strains that are resistant to conventional dosages of amoxicillin – clavulanate and levofloxacin.

### *Hemophilus influenza*

In elderly individuals, particularly those with underlying lung disease *H. influenza* can cause severe pneumonia. The development of  $\beta$ -lactamase negative ampicillin resistant strains (BLNAR) has been considered as an important advance in the evolution of these organism species since there is associated alteration of penicillin binding protein binding site. Prevalence of BLNAR among *H. influenza* has been increasing in various countries, including Asia (18.2%).<sup>[14]</sup>

### Atypical pathogens

Similarly in Asian population the high prevalence of atypical pathogens amongst CAP patients presents a unique challenge in empirical management.

Prescription event monitoring study is a well-established, noninterventive, observational tool of postmarketing surveillance (PMS) when giving or prescribing drugs in “real life” clinical practice, on a national level, including patients with comorbidities and concomitant medications.<sup>[15]</sup> A PEM was therefore conducted, to better understand the health outcome or safety profile of garenoxacin when administered in “real world” out-patient clinical settings of India. Importantly, in a PEM study, there is no need for the prescribing doctor to give an opinion about whether an “event” might have been caused by the drug. At the end of the observation period, this data would be submitted for subsequent analyses.

Garenoxacin is a newly developed quinolone in Japan that was further researched and developed by Toyoma Ltd., in collaboration with Bristol Meyers Squibb, USA. Drug Controller General of India (DCGI) has approved the use of garenoxacin on 07/06/2013 for the treatment of bacterial RTIs with permission no. MF-131/13 in form 46 under Drugs and Cosmetic Acts and Rules thereunder.<sup>[16]</sup> It was subsequently launched in India by Glenmark Pharmaceuticals Ltd.

Garenoxacin has been demonstrated to have excellent pharmacokinetics/pharmacodynamics (PK/PD) profile due to structural modification of the quinolone at 6<sup>th</sup>, 7<sup>th</sup> and 8<sup>th</sup> positions. This unique structure activity relationship offers one of the lowest MICs against respiratory pathogens coupled with complimentary lowering in potential for resistance development as reflected by low mutant prevention concentrations.<sup>[17]</sup>

Garenoxacin is therefore a welcome addition to the therapeutic armamentarium of the clinicians while treating some of the community-acquired RTIs, especially in “empirical” settings.

Under the clinical research program involving international collaborators, nearly 20 Phase I/II/III/IV trials with approximately 10,000 patients has been conducted with some of them published as late as in 2011.<sup>[18,19]</sup>

Garenoxacin mesylate has been well-tolerated in above clinical trials with its true character revealed in “real world clinic settings” or PMS studies.

In a clinical review of literature by Takagi *et al.*<sup>[18]</sup> involving clinical trials conducted between 2001 and 2004, garenoxacin was found to be safe and effective. Drug related adverse events were observed in 12.7% cases. The common adverse events were diarrhea (2.4%), nausea (1%) and headache (1%). All the events were of mild to moderate severity and did not require discontinuation of therapy.

However in a PMS study conducted by Hori and Maki<sup>[19]</sup> in “real-world outpatient settings,” safety records from 6412 patients were accessed. Garenoxacin use reported negligible incidence of gastrointestinal disturbances including diarrhea (0.5%), dizziness (0.05%), somnolence (0.06%) or hypotension (0.05%) thus offering a unique safety profile that is unparalleled among fluoroquinolones or  $\beta$ -lactams.

The current study once again demonstrated the superior safety profile of garenoxacin with negligible incidence of gastrointestinal, central nervous system and cardiovascular side-effects. Diarrhea was noted in 0.1% of the patients that is similar with the earlier reported incidence of 0.5% by Hori and Maki<sup>[19]</sup> None of the patients developed any serious cardiovascular reactions including QTc prolongation or torsades pointes at the end of the observation period.

Two failure cases were noted during the course of the observation period that was managed symptomatically with injectable  $\beta$ -lactam or ceftriaxone/tazobactam therapy that was administered in the outpatient setting without further need for hospitalization.

## CONCLUSION

Since the introduction of garenoxacin in India for the first time, this PEM study demonstrated the excellent tolerability and utility of the drug in varied clinical conditions, especially in community-acquired infections when administered as empirical choice. Garenoxacin with its superior yet differentiated PD and PK profile involving low MICs with high target site tissue

concentrations definitely finds a merit for further evaluation in other uncomplicated clinical conditions, including SSSTIs, UTIs, gastrointestinal infections and typhoid.

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