Clinical experience with clarithromycin prolonged-release (Fromilid uno) in the treatment of respiratory tract infections

Tanja Blatnik,
Nataša Lebar

Key words
macrolide antibiotics, clarithromycin, prolonged-release tablets, respiratory tract infections, clinical experience

Abstract
Broad antimicrobial spectrum covering the most common respiratory pathogens, good tolerability and simple administration are the main reasons why clarithromycin has been used extensively for empirical treatment of community-acquired respiratory tract infections.
We analyzed three phase IV clinical studies with Fromilid uno (clarithromycin prolonged-release) in the treatment of upper and lower respiratory tract infections and they confirmed its high bacteriological and clinical efficacy. In addition, very good tolerability and patient compliance were observed.
The results of our clinical experience together with the latest international guidelines support the use of clarithromycin for empirical treatment of respiratory tract infections.

Introduction

The first macrolide antibiotic discovered was erythromycin, which has been used since the early 1950s. However, frequent gastrointestinal intolerance and a short serum half-life, which requires four-times daily administration, have limited the use of erythromycin.[1, 2]

Clarithromycin is derived from erythromycin and differs from it by O-methyl substitution at position 6 of the lactone ring, which confers improved tolerability, pharmacokinetic properties, antimicrobial effect and a broader antimicrobial spectrum.[1, 3] The antimicrobial efficacy of clarithromycin is enhanced also by the *in vivo* formation of microbiologically active 14-hydroxy metabolite, which in combination with clarithromycin acts synergistically against a variety of pathogens, including *H. influenzae*.[3] Similarly to other macrolides, clarithromycin also exerts its antimicrobial effects by reversibly binding to the 50S subunit of the bacterial ribosome and thus inhibits RNA-dependent protein synthesis.[1] Macrolides, including clarithromycin, have time-dependent pharmacodynamics, so the length of time during which the concentration of the drug is above the minimum inhibitory concentration (MIC) is the most important parameter for determining clinical and microbiological efficacy. The goal of a dosing regimen for these drugs is to optimize the duration of exposure.[4]

Clarithromycin prolonged-release was developed to improve patient compliance by reducing dosing frequency as non-compliance is a significant problem in antibiotic therapy, often resulting in treatment failure and promoting antibiotic resistance. Therefore, antibiotic therapies which can be administered once daily (such as clarithromycin prolonged-release), improve compliance compared to multiple daily doses and consequently also treatment outcome.[5] Krka's clarithromycin prolonged-release tablets (Fromilid uno) were introduced in 2003.[6] Krka's experts developed own prolonged-release formulation, which is patent-protected.[7]

Prolonged-release formulation enables:

- lower fluctuations in plasma concentrations, while maintaining equipotent bioavailability[8]
- reduction of severity of gastrointestinal adverse effects and the frequency of discontinuation of therapy due to gastrointestinal discomfort or taste perversion[5]
- improved patient compliance[5]

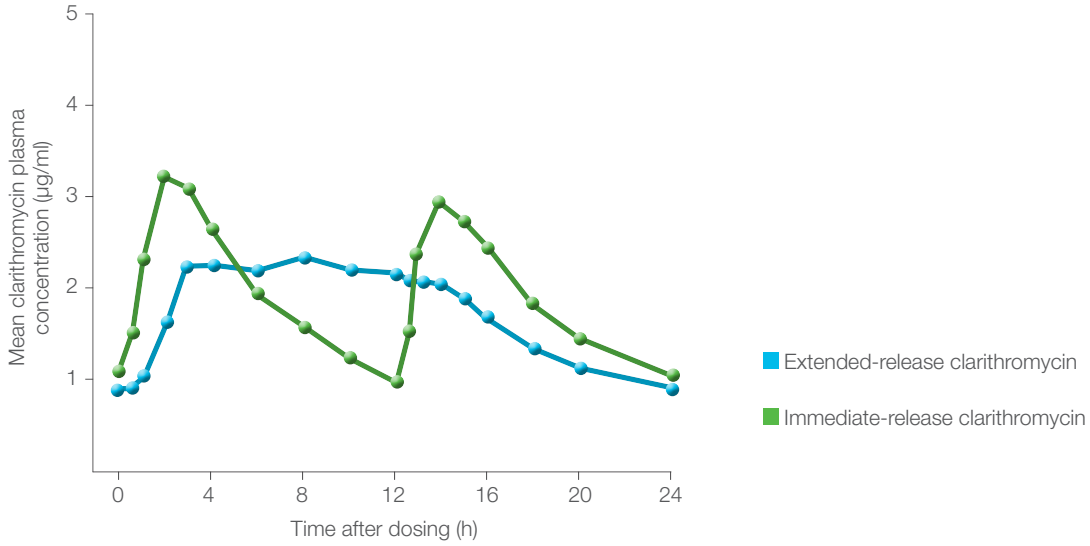


Figure 1. Pharmacokinetic analyses: mean steady-state (day 5) plasma concentration–time profiles for extended-release clarithromycin (1000 mg/day × 5 days) and immediate-release clarithromycin (500 mg twice daily x 5 days)[8]

Fromilid uno is indicated for the treatment of upper respiratory tract infections (e.g. tonsillopharyngitis, acute sinusitis), lower respiratory tract infections (e.g. acute bacterial bronchitis, acute exacerbations of chronic bronchitis (AECB), pneumonia), and skin and subcutaneous tissue infections.[9]

Clarithromycin exerts a number of positive effects on disease course which have not been directly related to its antibacterial effect, but are the result of its immunomodulatory and anti-inflammatory properties. These effects include a significant reduction in several parameters of inflammation, markedly reduction of inflammatory cell accumulation in bronchoalveolar lavage fluid, decreased airway hyper-responsiveness, reduction of sputum production and increased sputum elasticity in patients with chronic inflammatory lung diseases, and several others.[10–12]

Biofilms are most often found in the context with chronic or recurrent respiratory and urinary tract infections.[13] Studies have shown that clarithromycin (even in sub-inhibitory concentrations) prevents biofilm formation and thus contributes to eradication of microorganisms, which may create a biofilm.[13–15]

Laboratory surveillance data suggest that macrolide resistance among *S. pneumonia* has increased over the last decades.[16] However, despite the increasing prevalence of macrolide resistance among *S. pneumoniae*, clinical failures have been infrequently reported.[1, 16] So, what are the reasons for better outcomes than MICs alone might predict? One of the reasons why macrolide resistance might not prove clinically significant is the mechanism of resistance which involves either efflux pumps (actively transport macrolide out of bacteria) or ribosomal target site modification which inhibits macrolide binding. Efflux resistance is more common and relatively weak. Another reason is that macrolides (especially clarithromycin and azithromycin) concentrate more extensively within the respiratory tract than in the serum and have anti-inflammatory properties that enhance their efficacy.[16, 17] Despite the era of increasing macrolide resistance clarithromycin remains an important antibiotic for empirical treatment of respiratory tract infections.[16]

Clinical experience with Fromilid uno

The efficacy of Fromilid uno (500 mg clarithromycin prolonged-release tablets) has been examined in several phase IV clinical trials in the treatment of AECB, pneumonia, acute tonsillopharyngitis, acute sinusitis and acute otitis media. The dosage and duration of therapy varied according to the indication and the study. In all studies the primary endpoint was the clinical success rate.

Fromilid uno in the treatment of upper and lower respiratory tract infections

The first study[18] in which we evaluated the efficacy and safety of the treatment of acute respiratory tract infections with Fromilid uno was carried out in Slovenia. The statistical analysis comprised 1,044 patients. Fifty-five percent of the patients received Fromilid uno for the treatment of upper respiratory tract infections (acute pharyngitis or/and acute sinusitis) and 45% of the patients for lower respiratory tract infections (acute exacerbation of chronic obstructive pulmonary disease (AECOPD) or/and pneumonia).

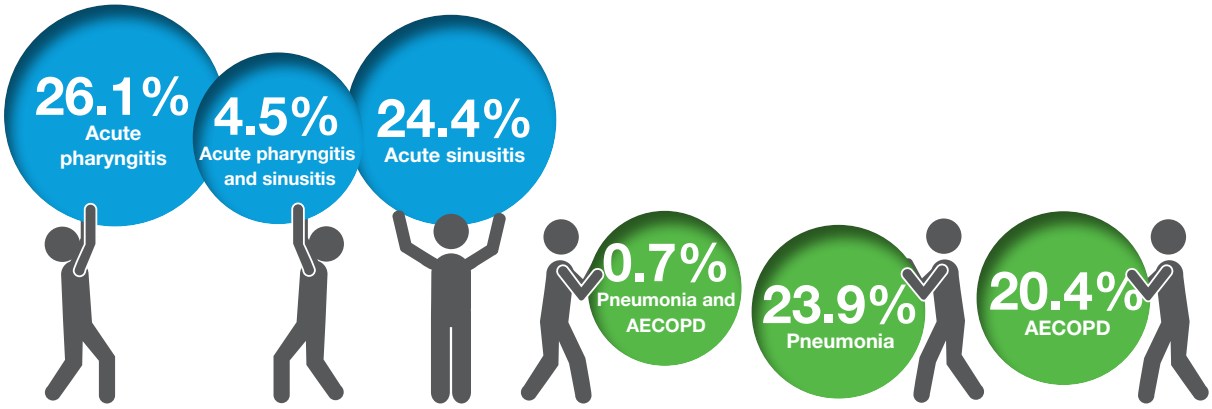
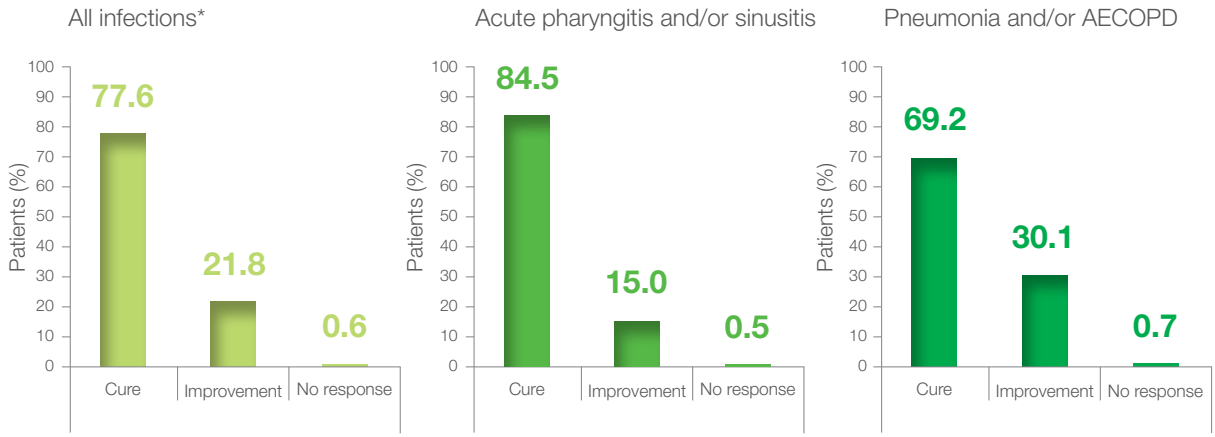


Figure 2. Percentage of patients with individual indications

The majority of patients (87%) were treated with one Fromilid uno tablet daily. Patients with pneumonia and those who suffered from pneumonia and AECOPD were most frequently treated with two Fromilid uno tablets daily and the duration of treatment in these patients usually exceeded the standard 7 days. Otherwise, the average duration of the treatment in all groups of patients was 8 days.

Fromilid uno demonstrated high clinical efficacy. Clinical success of the treatment (cure or improvement) reached 99.5% of patients with upper respiratory tract infections and 99.3% of patients with lower respiratory tract infections.

The treatment with Fromilid uno tablets was well tolerated; there were only 77 patients (7.4%) who experienced adverse reactions, most of which were mild. The most commonly reported adverse reactions were gastrointestinal problems (in 4.3%), and bitter taste (in 2.0%).
Thirteen patients (1.2%) withdrew from treatment due to adverse effects. Their treatment was discontinued due to gastrointestinal adverse effects, nausea, vomiting or bitter taste, which in most cases were of moderately severe intensity.
The adverse effects were characteristically more common with the larger dose (1000 mg) of Fromilid uno.



* including upper and lower respiratory tract infections

Figure 3. Clinical efficacy in acute respiratory tract infections with Fromilid uno

FORWARD study (Efficacy and safety of the medicine Fromilid uno in patients with purulent-inflammatory diseases of ENT organs)

The aim of the FORWARD study[19] was to evaluate clinical and bacteriological efficacy of the treatment with Fromilid uno in patients with upper respiratory tract infections (acute tonsillopharyngitis, acute sinusitis and acute otitis media). An additional aim was to evaluate the tolerance of Fromilid uno therapy and patient compliance.

The analysis of the efficacy and safety of Fromilid uno in 150 patients with upper respiratory tract infection was performed in three groups of patients: patients with acute tonsillopharyngitis (group 1), acute sinusitis (group 2) and acute otitis media (group 3). In each group 50 patients were included in accordance with inclusion criteria. Fromilid uno was administered in two dosages: 1 tablet (500 mg) per day in patients with acute tonsillopharyngitis and 2 tablets (1000 mg) per day in patients with acute sinusitis and acute otitis media. The duration of therapy was 7 days. According to the study protocol all patients were monitored during a 10-day period. The evaluation of the efficacy of the therapy was performed at visit 2, 3 and 4. The condition of each patient was evaluated as: deterioration, no changes, significant improvement or clinical recovery.

All patients with acute tonsillopharyngitis had positive results for the presence of group A β-hemolytic streptococcus (GAS). Additionally, a bacteriological analysis of the oral mucus smears was performed. GAS was isolated in 44 patients (88%) and all isolated GAS strains were sensitive to clarithromycin. Other epidemiologically significant bacterial species were present with individual strains. In the repeated bacteriological analysis on day 7 of therapy, GAS strains were observed only in 4 cases, which means that the eradication of GAS was 91%. Clinical recovery was achieved in 95.9% of patients with acute tonsillopharyngitis.

Before the start of antibiotic therapy, bacteriological analysis of the sinus content was performed in 44 patients with acute sinusitis. Bacterial growth was observed in 36 patients (82% of the tested patients). The predominant species was *S. aureus*, followed by *S. pneumonia* and *H. influenzae*. Other bacterial species, including enterobacteriaceae, were present in individual strains. Repeated bacteriological analysis showed that bacteria were not eradicated in 4 patients. Accordingly, bacterial eradication was achieved in 88% of cases. Clinical recovery was achieved in 79.6% of patients with acute sinusitis.

Diagnostically significant material for microbiological analysis was observed only in 6 patients with acute otitis media. In further studies bacterial growth was observed just in 5 samples.

Isolated bacteria were *P. aeruginosa* and *S. aureus*. All strains of *P. aeruginosa* were resistant to clarithromycin, while the strains of *S. aureus* were sensitive. The percentage of patients who were clinically cured was 79.2% and 16.7% had significant improvements.

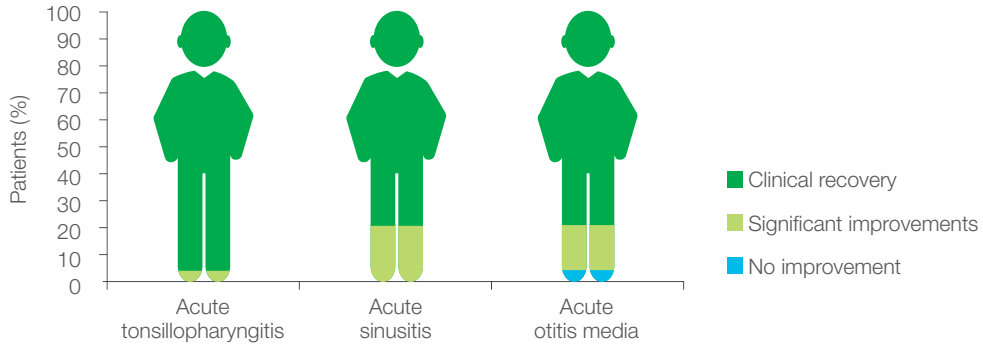


Figure 4. Clinical efficacy of Fromilid uno in the treatment of upper respiratory tract infections

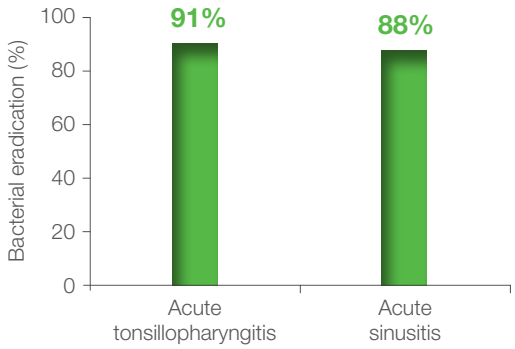


Figure 5. Antimicrobial efficacy of Fromilid uno in the treatment of upper respiratory tract infections

During the study the tolerance of Fromilid uno was evaluated. Electrocardiographic analysis did not reveal any statistically significant changes in the rhythm during the medicine intake. Four patients were excluded from the study: two due to dyspeptic disorders, one hypertensive patient due to destabilization of arterial blood pressure and one patient with infectional mononucleosis that was established later on. Otherwise, a very good tolerability of Fromilid uno was observed. The compliance in all patients during the study was 100%.

Fromilid uno in the treatment of acute sinusitis

Each year 1 to 5% of adults in Europe are diagnosed with acute sinusitis by their general physicians. The usual causative pathogens are *S. pneumoniae* and *H. influenzae*, occasionally also *M. catarrhalis*. The trigger for acute bacterial sinusitis is often a previous viral upper respiratory tract infection, with approximately 50% of common colds becoming complicated with the development of acute sinusitis.[20]

Fifty patients with mild to moderate acute bacterial maxillary sinusitis and with the average age 36.5 (±4.7) years were included in the phase IV clinical study[21] conducted in 2012 in Russia. In all patients bilateral maxillary sinuses puncture was performed, revealing purulent or mucopurulent lavage fluid. In all 50 patients frontal rhinoscopy showed hyperemia, mucosal edema, and pathological discharge of purulent or mucopurulent nature. According to X-ray results homogenous opacity and fluid level in the affected sinuses were observed in all 50 patients.

Clinical success was defined as an improvement of the patient's condition and reduction of the severity of clinical symptoms of acute sinusitis over 2 days (maximum daytime body temperature below 37°C, absence of purulent nasal discharge, absence of purulent sinus discharge in rhinoscopy).

Patients were treated with Fromilid uno 500 mg tablets once daily for 7 to 10 days, depending on the dynamics of disease symptoms. All the included patients completely met the inclusion criteria and completed the study.

In order to assess bacteriological efficacy sinus punctures were performed also on day 3, 5, 7 and 9.

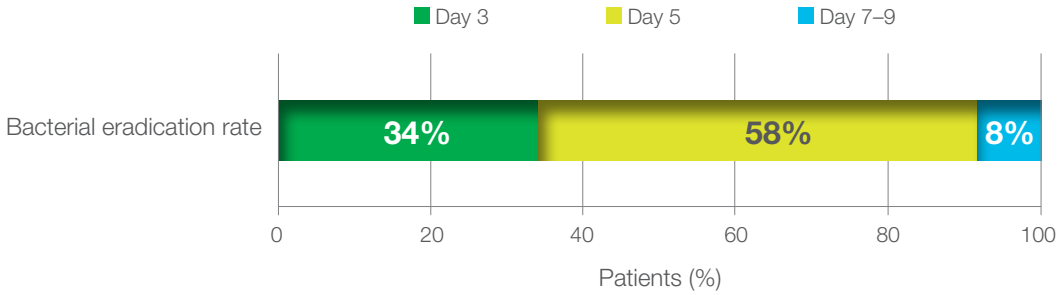


Figure 6. Clear lavage fluid in maxillary sinuses puncture was obtained in 17 patients (34%) on day 3, in 29 patients (58%) on day 5, in 2 patients (4%) on day 7 from the beginning of the treatment and in 2 patients (4%) on day 9.

According to the study protocol the bacteriological analysis was performed in 39 patients. The most frequently isolated pathogens were: *S. pneumoniae* (41.2% of patients) and *H. influenzae* (32.3% of patients). Other isolated pathogens were: *S. pyogenes*, *S. aureus, M. catarrhalis, Staphylococcus* spp. and others. Eradication of pathogens or a significant reduction of their quantitative composition was achieved in all patients. Clinical efficacy was in accordance with bacteriological results. Treatment with Fromilid uno resulted in marked clinical improvement in all patients.

The most frequently reported adverse reaction was diarrhea. In total, adverse reactions were mild and transient and required no treatment withdrawals. During the study the investigators noticed positive patients' response to the frequency of administration of Fromilid uno and concluded that Fromilid uno is patient-friendly and well tolerated, which significantly increased treatment compliance.

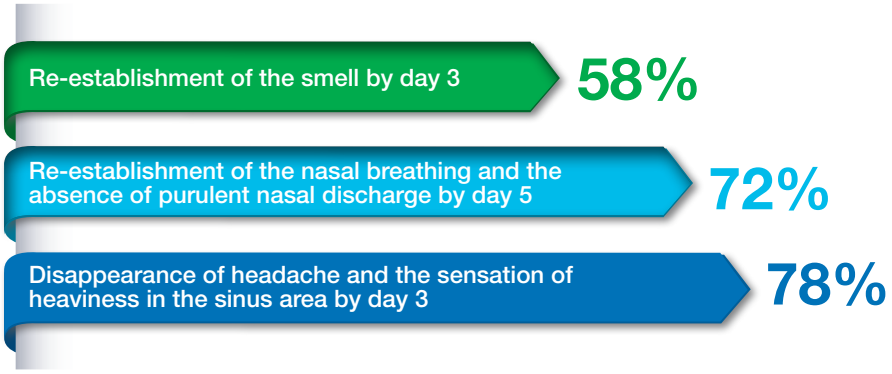


Figure 7. Relief of symptoms of acute bacterial sinusitis occurred in 3 to 5 days of treatment with Fromilid uno in the majority of patients.

Conclusions

Krka has engaged in the management of infectious diseases since its foundation in 1954. Apart from Fromilid uno, our antibiotic portfolio also includes two additional macrolides (Azibiot and Macropen), broad spectrum penicillins (Hiconcil, Betaklav), and fluoroquinolones (Nolicin, Ciprinol, Moloxin[A]). Confidence in Krka's antibiotics is reflected in the several millions of treated patients. So far, over 7 million patients have been treated with Fromilid uno alone. In more than 10 years of clinical experience with Fromilid uno, several phase IV clinical studies have been performed, including almost 11,000 patients. In this review we have taken a closer look at three of them. All these studies confirmed high bacteriological and clinical efficacy of Fromilid uno in the treatment of upper and lower respiratory tract infections. Its good tolerance and simple once daily administration increase treatment compliance, which is crucial for successful antibiotic therapy.
The main reasons for wide clinical utility of clarithromycin are its high clinical efficacy, simple administration, good tolerance, efficacy against most common respiratory tract pathogens and a number of other positive effects on disease course which are not directly linked to its antimicrobial efficacy. Due to all its properties clarithromycin keeps an important position in the empirical treatment of community-acquired respiratory tract infections.

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[A] The product is marketed under different names in different countries (Moloxin, Moflaxa, Moflaxya, Moxibiot).

Authors

Tanja Blatnik, MPharm
Krka, d. d., Novo mesto, Dunajska cesta 65, 1000 Ljubljana, Slovenia

Nataša Lebar, MPharm
Krka, d. d., Novo mesto, Dunajska cesta 65, 1000 Ljubljana, Slovenia

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