

# Novel, single-dose microsphere formulation of azithromycin extended-release for the treatment of respiratory tract infections

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This paper reviews the pharmacology, efficacy and safety of the new single-dose azithromycin 2 g extended-release microsphere formulation that has been approved in various countries for the treatment of a variety of upper and lower community-acquired respiratory tract infections. As it has been demonstrated to be at least as effective and safe as valid, contemporary comparators, this new single-dose formulation of azithromycin offers the first treatment option for respiratory tract infections that lends itself to 100% patient compliance and regimen completion.

Antimicrobials typically recommended and utilized for the treatment of suspected or documented mild-to-moderate bacterial community-acquired respiratory tract infections (RTIs) in adults, such as  $\beta$ -lactams, fluoroquinolones, doxycycline, and most macrolides, usually require a 5–21-day regimen involving daily or more frequent dosing. The one exception to this rule to date has been azithromycin, which has been historically dosed once daily for 3–5 days for the same indications. These short, once-daily azithromycin courses have most certainly improved patient compliance with taking and completing a whole course of therapy for RTIs. However, the obvious best possibility for 100% patient compliance and/or completion would be a single-dose RTI treatment. Although historically single-dose treatments for a systemic infection have been used for the treatment of uncomplicated urinary tract infections (i.e., high-dose amoxicillin, fosfomycin), this has not been thought possible for RTIs until relatively recently.

In an open-label, randomized study by Schönwald and colleagues, the efficacy and safety of a single, oral 1.5-g immediate-release (IR) dose of azithromycin was compared with the standard European 3-day azithromycin regimen (500 mg/day) in the treatment of community-acquired atypical pneumonia (atypical CAP) [1]. Subjects ( $n = 100$ ) ranged 16–86 years of age and were equally randomized to the azithromycin treatment regimens. Signs and symptoms of pneumonia were evaluated before and at 72 h, 10–14 days and 4 weeks after the start of treatment to assess clinical efficacy. Although 50% were infected with an unknown pathogen(s), the remaining patients were infected with common atypical CAP pathogens such as *Mycoplasma pneumoniae*, *Chlamydomphila* spp.,

*Legionella pneumophila* and *Coxiella burnetii* or a combination thereof. At the end of the study, 48 subjects in each group were evaluable, with each group having 47 cured (97.9%). Both study regimens were well tolerated with two patients in the single-dose and one patient in the 3-day group experiencing drug-related side effects [1].

In a second open-label, equal randomization study by the same investigators, a single IR dose of azithromycin 1.5 g was compared with the 3-day azithromycin regimen and a 10-day twice-daily clarithromycin regimen (250 mg/dose) in 178 adult (>18 years of age) atypical CAP patients [2]. Signs and symptoms of pneumonia were evaluated at baseline and repeated at 48 and 72 h, 10–14 days and 4–5 weeks after treatment initiation. In this study, 50–60% of patients were infected with *M. pneumoniae* and approximately 8% were infected with *C. pneumoniae*, with the majority of the remaining patients being infected with an unidentified pathogen (~32%). Clinical cure (defined as pneumonia sign/symptom resolution and regression of infiltrate on chest radiograph) rates were 100% (60/60) for the IR single-dose azithromycin group and 98.6% for the 3-day azithromycin (56/58) and 10-day clarithromycin (58/60) groups. Drug-related adverse events were reported by only one patient in the clarithromycin group, and nine, ten and 12 patients respectively were discovered to have mild transaminase rises and/or eosinophilia [2].

In a separate, noncomparative pilot study by Karpov and colleagues, ten adults with clinically and bacteriologically confirmed diagnoses of uncomplicated tonsillitis were administered 1.5 g of IR oral azithromycin as a single-dose regimen [3]. Follow-up evaluations were performed on days 3, 10, 30 and 60 after administration of

**Keywords:** azalide,  
azithromycin, macrolide,  
pneumonia, sinusitis



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azithromycin. Resolution of fever occurred on day 2 of the study in seven of ten patients and on day 3 in the remainder of the patients. Mean clinical scores (system not defined) was 14.1 before treatment, 7.8 on day 3 and had decreased to 0.8 by day 10 after drug administration. No patients demonstrated any signs or symptoms of early or late rheumatic complications and none of the patients reported any adverse events associated with the regimen [3].

The fact that these single-dose IR azithromycin regimens were effective for these RTIs, especially CAP, was not very surprising and potentially even expected when the pharmacokinetics of the various 1.5 g IR regimens are taken into account. Studies in healthy volunteers have demonstrated serum/plasma and phagocyte (neutrophils and macrophages) exposures that are at least equivalent when 1.5 g of oral IR azithromycin is administered as a single whole dose compared with when divided over the standard 3- and 5-day marketed regimens [4,5]. In fact, these data actually demonstrate that although not significantly so, the larger and albeit fewer doses the entire regimen is administered as, the higher a volunteer's exposure to the drug becomes [4,5].

Animal model data have also since been presented which suggest that single-dose azithromycin regimens may even be superior in terms of efficacy and time to efficacy. As an example, in a study by Girard and colleagues, the efficacy of a large single dose of azithromycin was evaluated in comparison to the same dose divided over 2 or 3 days in various animal infection models [6]. In an acute peritonitis model, mice were inoculated with *Streptococcus pneumoniae* (penicillin/macrolide susceptible), *S. pyogenes* (macrolide susceptible), *Enterococcus faecalis* (vancomycin susceptible) or *Haemophilus influenzae* (penicillin/macrolide susceptible and penicillin resistant/macrolide susceptible strains) and then administered the azithromycin regimens starting 0.5 h post-inoculation. In a pneumococcal pneumonia model, mice were treated with the regimens starting 18 h post-inoculation to allow for bacteremia to be established. In an acute otitis media model using *H. influenzae*, gerbils were dosed the regimens starting 18 h after inoculation. The single-dose regimens of azithromycin in the mouse models demonstrated superior survival and eradication rates compared with when the same total dose was split over 2 or 3 days. In the otitis gerbil model, the single dose of azithromycin sterilized the middle ear and more rapidly eradicated the pathogen than the split-dose regimens [6].

A similar study was performed by Kamicker and colleagues, using murine pneumococcal pneumonia and gerbil *H. influenzae* otitis models in which either 100 mg/kg or 100 and 200 mg/kg, respectively, azithromycin regimens were administered as either a simulated single sustained-release (SR) dose, a single IR dose or split over 3 or 5 days [7]. The results of the pneumococcal pneumonia model demonstrated that both SR and IR single-dose regimens provided significantly better survival results than if the total dose were split over a 3- or 5-day period. In the otitis model, the 100 mg/kg SR and IR single-dose regimens had 100% eradication by day 7 compared with only 40–50% eradication for the 3- and 5-day regimens. The 200 mg/kg SR single dose regimen demonstrated 100% eradication by day 2, which was in contrast to the 60–70% eradication rates demonstrated with the 3- and 5-day regimens [7]. Based on these studies, it is not only evident that patients receive at least the same amount of drug if it is administered as a single, total dose but also that the front-loading effect may actually be beneficial in terms of clinical and microbiological efficacy compared with splitting the total dose over multiple days.

However, what was surprising from the initial adult IR single-dose human efficacy studies was the lack of adverse events reported, especially gastrointestinal (GI) [1–3]. It has been repeatedly demonstrated that the side-effect profile, especially in terms of GI adverse events, significantly increases when single IR azithromycin doses of more than 1.2 g are administered even in a fed state (>35% incidence vs <10% with ≤1 g IR doses). Therefore, the lack of side effects in the above studies does not seem possible and is most likely due to cultural issues in terms of reporting side effects rather than a true lack of occurrence [1–3,8–10].

Based on these data, it was necessary to develop a way to achieve the potential enhanced compliance, clinical and microbiologic efficacy benefits that might be associated with a single-dose azithromycin regimen, but with an adverse effect profile similar to that experienced with the marketed 3- and 5-day RTI regimens. This end point was realized by formulating azithromycin in an extended-release (ER) microsphere marketed as a 2 g single-dose oral suspension (Zmax™) that is reconstituted with 60 ml of water and should be taken within 12 h of reconstitution. To date, this formulation is available in the USA for the treatment of mild-to-moderate outpatient CAP and acute bacterial sinusitis

(ABS). In the Philippines and Mexico (it is under review in a number of additional markets) it is also approved for the additional indications of acute exacerbations of chronic bronchitis (AECB) and streptococcal pharyngitis in adults. The following sections of the paper will be dedicated to a review of this new formulation.

## Extended-release formulation

### *Pharmacokinetics*

The pharmacokinetics of the 2 g ER azithromycin suspension have been characterized in healthy adult volunteers and compared with those achieved by the administration of 2 g of IR suspension (2 × 1 g powder for oral suspension sachets) and with the standard 1.5 g total dose IR 3- and 5-day regimens [11,12]. As would be expected, the peak serum concentration ( $C_{\max}$ ) from the 2 g ER dose was higher than that experienced with the 500 mg day 1 IR doses used in the 3- and 5-day regimens (0.821 vs 0.441 vs 0.434 mg/l, respectively). As desired, the front-loading effect was pharmacokinetically evident as the 24 h exposure ( $AUC_{24}$ ) of the 2 g ER dose was three to four times as high as that experienced with the 500 mg IR day 1 doses of the 3- and 5-day regimens (8.62 vs 2.58 vs 2.6 mg/h/l, respectively). This was in contrast to the overall exposure ( $AUC_{\infty}$ ) to the regimens where the slightly higher total dose of the 2 g ER regimen provided a total exposure that was only about 33% higher than that experienced with either of the 1.5 g total dose IR regimens (20.0 vs 17.4 vs 14.9 mg/h/l). The time to  $C_{\max}$  ( $T_{\max}$ ) was approximately twice that associated with the 500-mg IR doses of the 3- and 5-day regimens (5.0 vs 2.5 vs 2.5 h, respectively) which is not surprising based on the ER properties of this formulation. When the same 2-g total dose was compared between the ER and IR formulations, the differences noted are again not unexpected. For instance, the ER nature of the new product results in a  $C_{\max}$  57% lower than that of the 2 g IR suspension administered. The 17% decrease in overall exposure when administered as the 2 g ER form compared with the IR product may be due to the significant variability seen in the pharmacokinetics of azithromycin even between healthy volunteers. It may also be due to the immediate availability of the IR dose as opposed to the prolonged release of the ER dose and azithromycin's tendency to have greater relative bioavailability as at least IR doses increase. Regardless of the reasons behind these differences, the comparison of the 2 g ER and IR suspension doses demonstrates that it is not possible to

substitute two of the 1g IR powders for oral suspension sachets for the new 2 g ER microsphere suspension dose [11].

Although the majority of food–drug interactions involve the food decreasing the bioavailability of a dose of a drug, the opposite has been noted with the azithromycin 2 g ER microsphere formulation. With both high- and low-fat meals (~60 and 36% of kcal from fats, respectively) there appears to be a dose-dumping effect induced by the food which results in  $C_{\max}$  values increasing by over 100%, although the impact on total exposure is significantly more muted (~23% increase) [11]. Since the extent and rate of absorption from the 2 g ER suspension is not affected by coadministration with an aluminum/magnesium antacid, the underlying cause appears to be something other than the minerals that may be present in a meal. Regardless of the cause, as this marked increase in  $C_{\max}$  would most likely result in a significantly greater incidence of GI side effects, which the ER formulation was designed to avoid, dosing recommendations state that the drug should be administered either 1 h prior to or at least 2 h after meals [11].

### *Safety & efficacy*

Although approved indications for the azithromycin 2 g ER microsphere formulation may vary from country to country, it has been compared with valid references for a variety of RTIs.

### *Community-acquired pneumonia*

CAP continues to be a common and serious illness despite treatment advances. Although overall it is the sixth leading cause of death in the USA, mortality associated with mild-to-moderate CAP appropriate for outpatient treatment is low with a less than 1% incidence [13,14]. Macrolides, alone or in combination with a  $\beta$ -lactam (if patient had recent antibiotic therapy), are still considered one of the first-line treatment options for CAP regardless of whether the patient does or does not have potentially complicating comorbidities (chronic, obstructive pulmonary disorder [COPD], diabetes, renal or congestive heart failure, malignancy) [14].

In support of this new azithromycin dosing regimen, a randomized, double-blind, placebo-controlled, multicenter study was conducted to determine whether the single dose of azithromycin 2 g ER microsphere formulation was as effective as a 7-day course of levofloxacin (500 mg/day) in the treatment of mild-to-moderate CAP (Fine classes I–III) [15]. Eligible

patients were observed as they received their first dose and then assessed for efficacy at both days 14–21 and 28–35. As would be expected with a single-dose regimen, patients receiving the ER azithromycin microspheres were 100% compliant. Compliance with the 7-day levofloxacin regimen was approximately 95%. Of the 211 ER azithromycin- and 212 levofloxacin-treated patients, 174 and 189 were eligible for clinical efficacy assessment, respectively. Clinical cure rates for the groups were 89.7 and 93.7% (95% confidence interval [CI]: -9.7, 1.7), respectively, with only one (0.5%) patient in the levofloxacin group considered a relapse at the long-term follow-up visit. Of the 91 and 104 respective bacteriologically evaluable patients eradication was documented or presumed in 90.1 and 92.3% of patients, respectively. The most common adverse effect was diarrhea in both groups, with an incidence of 12.7% in the azithromycin group and 4.7% in the levofloxacin group; however, 85% of those who experienced diarrhea in the azithromycin group stated that the diarrhea was limited to the dosing day and/or the following day. Based on these results, the authors correctly concluded that the single dose of azithromycin 2 g ER microspheres was as effective as a 7-day course of levofloxacin in treating mild-to-moderate CAP [15].

In a separate randomized, multicenter, double-blind, double-dummy trial 499 patients with Fine class I or II CAP received either a single dose of azithromycin 2 g ER microspheres or a 7-day course of clarithromycin ER (1g/day) [16]. The first doses of the assigned regimens were observed by investigators and response was evaluated at days 14–21 and 28–35. Of the 202 azithromycin and 209 clarithromycin clinically evaluable patients, cure rates were 92.7 and 94.7% (95% CI: -6.9, 2.6), respectively. Relapse rates for the two regimens at the long-term follow-up visit were 0.6 and 2.8%, respectively. Bacteriologic eradication rates overall were similar at 91.8% (123/134 subjects) and 90.5% (153/169 subjects), respectively. Although of small incidence, it is interesting to note that the difference in *Moraxella catarrhalis* eradication where azithromycin achieved 100% eradication (8/8) whereas clarithromycin only achieved 60% eradication (3/5). There was 100% compliance with the single-dose ER azithromycin part of the regimen as opposed to approximately 92% compliance with the subsequent 6-day placebo regimen the azithromycin-randomized patients received. Compliance with clarithromycin was approximately 94%. The

incidence of adverse events was essentially equal between treatment arms with the highest incidence involving mild-to-moderate diarrhea/loose stools (12.1 vs 7.5%, respectively). As before, half of those receiving azithromycin reported symptoms abating on day 1 or 2 of the study. Based on these results, it was appropriately concluded that the single dose of azithromycin 2 g ER microspheres was equivalent and as well tolerated as a 7-day course of ER clarithromycin in the treatment of mild-to-moderate CAP [16].

It can be concluded from these studies that not only does the single-dose azithromycin ER microsphere formulation offer an equally efficacious and well-tolerated option as levofloxacin and clarithromycin, but it also provides an option that offers superior regimen compliance and completion. Whether the use of this formulation should be restricted to mild-to-moderate outpatient CAP treatment has yet to be studied. That being said, it seems a logical extrapolation and next research step to investigate its use as part of combination regimens (i.e., daily intravenous ceftriaxone with a single 2 g oral azithromycin microsphere dose on day 1 of ceftriaxone) for the treatment of patients with CAP that have more significant symptoms and who require in-patient care. The overall cost of this regimen would most likely be significantly less than mono- or combination fluoroquinolone therapies, commonly used in many institutions at present.

#### *Acute bacterial sinusitis*

In the USA, approximately 20 million cases of ABS are reported every year. Since diagnosis tends to be empirical, initial coverage requires known efficacy against typical causative pathogens such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* [17]. Typical first-line agents include extended-spectrum fluoroquinolones and high-dose amoxicillin or amoxicillin/clavulanate, with azithromycin recommended for those patients with a  $\beta$ -lactam allergy [17].

Similar to other azithromycin dosing regimens, the single dose of azithromycin 2 g ER microspheres also has this indication in adults. Support for this indication with the new formulation is evidenced by the study by Murray and colleagues in which the single dose of azithromycin 2 g ER microspheres was compared with a 10-day course of levofloxacin (500 mg/day) in 507 (256 and 251, respectively) patients with a clinical and radiographic diagnosis of ABS [18]. Patients underwent a baseline maxillary sinus aspiration and were

equally randomized to treatment in a double-blind, placebo-controlled fashion. Clinical cure rates at the test-of-cure visit (days 17–24 after first dose) were 94.5% for the single-dose azithromycin ER regimen compared with 92.8% with levofloxacin (95% CI: -2.5, 5.9%).

Of those patients culture positive at baseline 97.1% (99/102) of azithromycin and 91.9% (102/111) of levofloxacin patients were considered bacteriologic cures. When broken down by pathogen, eradication rates with azithromycin and levofloxacin, respectively, were as follows: *S. pneumoniae* 97.3% (36/37) and 92.3% (36/39); *H. influenzae* 96.3% (26/27) and 100% (30/30); and *M. catarrhalis* 100% (8/8) and 90.9% (10/11). Compliance with the azithromycin regimen was 99.6% compared with 96.3% with levofloxacin, and clinical cure rates in those patients that were compliant were essentially equal (91.1 vs 90.0%, respectively). The incidence of side effects with the two regimens was essentially equal at 23.3 and 15.3%, respectively, with the only main difference being incidence of diarrhea, which was 11.1% with azithromycin and 1.9% with levofloxacin. Although higher with azithromycin, most cases resolved in only 1–2 days. As demonstrated by this study, the single dose of azithromycin 2 g ER microspheres is at least equally efficacious to that of a 10-day course of levofloxacin which is one of the most commonly prescribed treatments for ABS at this time.

#### *Acute exacerbations of chronic bronchitis*

COPD is commonly encountered by practitioners in the USA and estimated to affect 12–15 million people [19]. Patients are susceptible to AECB which increases both the morbidity and mortality associated with their chronic disease state. Azithromycin has been used successfully for over 10 years worldwide for the treatment of AECB and the new single-dose azithromycin ER microsphere formulation has already received marketing approval in some of these countries. Zervos and colleagues studied the effect of this formulation in 542 older AECB patients (>50 years) with Anthonisen Type I exacerbations who were equally randomized and treated with either the single dose of azithromycin 2 g ER microspheres or 7-days of levofloxacin (500 mg/day) in double-blind, placebo-controlled fashion [19]. Clinical cure in evaluable patients (n = 438: 220 azithromycin, 218 levofloxacin) at the test-of-cure visit on days 14–21 after the start of treatment was achieved in 93.6% of those that

received azithromycin and 92.7% of those that received levofloxacin (95% CI: -3.4, 5.5). Baseline bacterial pathogens were identified in 48.5% of patients. Eradication rates for the two treatments were 91.9 and 94.4% (95% CI: -8.8, 3.8), respectively. Clinical cure by pathogen was as follows: *S. pneumoniae* 95 and 100%; *H. influenzae* 94.7 and 90.5%; and *M. catarrhalis* 92 and 81.3%. Although compliance was similar when both 7-day active/placebo regimens were examined, compliance with drug alone was 95% with levofloxacin as opposed to 100% with azithromycin. Similar to the previously described studies, treatment-related adverse effects were no different between treatment regimens overall (24 vs 15%, respectively). When examined by symptom, the only difference was again loose stools/diarrhea where the incidence was 12.3% for azithromycin vs 1.5% with levofloxacin; however, the majority of azithromycin-related cases resolved within 1 day [19]. Based on these results it is evident that when compared with one of the most commonly used treatments, levofloxacin, the new single dose of azithromycin 2 g ER microspheres is at least as efficacious and safe, with potential benefits in terms of regimen compliance and completion.

#### Expert commentary

The above data demonstrate that this unique formulation of azithromycin does indeed provide effective and safe treatment for a variety of outpatient upper and lower RTIs that is comparable to other commonly recommended and used antibiotics. As such, it would be expected that this single-dose regimen of azithromycin would provide clinicians the greatest possibility of assuring 100% compliance and regimen completion and that any clinical failures are more likely due to inappropriate coverage (i.e., patient had viral infection, or infection with a nonspectrum bacterial pathogen), resistance or reinfection/superinfection.

#### Outlook

The introduction of this novel oral dosage formulation/regimen of azithromycin comes approximately 10–15 years after the introduction of azithromycin and the other advanced-generation macrolides which have been so heavily and successfully used for the treatment of community-acquired RTIs. Despite past and present reports of growing international *in vitro* macrolide resistance, especially in terms of pneumococcal isolates, azithromycin and the

### Highlights

- A single dose of azithromycin 2.0 g extended-release (ER) microsphere formulation has been found to be at least as safe and effective as typical 7–10-day regimens of levofloxacin and clarithromycin for the treatments of community-acquired pneumonia (CAP), acute bacterial sinusitis (ABS) and acute exacerbations of chronic bronchitis (AECB).
- Clinical cure and eradication rates among patients with typical and atypical pathogens are at least comparable between the single dose of azithromycin 2 g ER microspheres and its comparators, levofloxacin and clarithromycin, in the treatment of outpatient CAP, ABS and AECB.
- The single dose of azithromycin 2.0 g ER microspheres is as well tolerated as its comparators overall. Like many other antibiotics, diarrhea/loose stools are the most common adverse effect; however, they tend to be mild-to-moderate in nature, lasting for only 1–2 days following dosing as opposed to for a prolonged period as is commonly encountered by patients during standard antibiotic courses that suffer from this side effect.
- The single dose of azithromycin 2 g ER microspheres offers the first effective and well-tolerated option that may result in 100% compliance and regimen completion for the treatment of community-acquired respiratory tract infections.

other macrolides continue to be used successfully in the clinical setting, even in areas of the world that have the worst incidences of resistance [20,21]. This, combined with the fact that mortality is consistently lower in those that receive a macrolide-containing regimen for CAP, this will result in the macrolides continuing to be of significant use in the treatment of community-acquired RTIs. In addition, these issues are also likely to keep azithromycin and the macrolides recommended in treatment guidelines as first- or second-line treatments alone or in combination with other agents for a variety of community-acquired RTIs. Whether the single-dose formulation of azithromycin can be used beyond out-patient treatment will require studies into its potential as part of a simplified in-patient RTI regimen as mentioned above.

Not only is this azithromycin formulation an attractive RTI treatment option, but it also lends itself nicely to trials that are investigating the immunomodulatory effects of azithromycin and the macrolides for chronic inflammatory pulmonary diseases where to date outcomes have been varied but always positive to some degree [21]. Due to the unique properties of the single-dose azithromycin ER microsphere formulation, it is possible that these trials may be able to utilize a single dose of this microsphere formulation once weekly or even less frequently to enhance patient satisfaction. However, the required frequency will have to be studied against the IR azithromycin regimens that are currently being studied to determine how infrequent dosing with the microspheres could be without losing the benefits demonstrated with the IR regimens.

As macrolides are known to be biofilm-active agents, another area of research could be to determine whether a single dose of the azithromycin microsphere formulation to dissolve away a patient's biofilm could be combined with antibiotics that are active against the actual biofilm-related pathogen. The investigation of this approach is very promising in light of our awareness of the prevalent and widespread nature of biofilm-related infections combined with their associated morbidity and mortality.

### Disclosure

Maya Tatum has no potential conflicts. Guy Amsden is a macrolide researcher, speaker and consultant for Pfizer Inc. and Pliva dd and has carried out antimicrobial research for Abbott Laboratories, Aventis, Bayer, GlaxoSmithKline and Bristol-Myers Squibb.

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