



## IND/NDA APPLICATION NUMBER(S)

Dear Sponsor:

Reference is made to your New Drug Application 50-710 for Zithromax® (azithromycin) for Oral Suspension. To obtain needed pediatric information on the use of oral azithromycin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act, that you submit information from studies in pediatric patients described below.

**Rationale:**

Genital infection with *Chlamydia trachomatis* (CT) is the most commonly reported sexually transmitted disease in the U.S. Because of the high prevalence of CT infection in women of childbearing age, it is estimated that more than 100,000 newborn babies are exposed during the birth process annually. An infant born to a woman with an untreated or inadequately treated genital CT infection is at considerable risk for acquiring the organism, particularly during vaginal delivery. CT is acquired in approximately 50% of infants born vaginally to infected mothers and has been reported in infants delivered by cesarean section with intact membranes. Results from existing studies indicate that the risk of developing conjunctivitis ranges from 8 to 44%, and the risk of developing pneumonia ranges from 0 to 17% in those infants who are exposed to CT at birth. The mean rates calculated from those studies are 15% for conjunctivitis, and 7% for pneumonia.<sup>(1)</sup> Conjunctivitis most often occurs during the first two to three weeks after birth, and pneumonia most often occurs between two weeks and three months of age, with a peak incidence of pneumonia between six and nine weeks of age. Antecedent conjunctivitis is not always present.

Recommended treatment by the American Academy of Pediatrics (AAP) Committee on Infectious Diseases in 2003 for CT conjunctivitis and pneumonia includes a 14-day course of orally administered erythromycin, given in four divided doses daily.<sup>(2)</sup> In 1997, the AAP also recommended prophylactic antimicrobial treatment with erythromycin of infants exposed to CT at delivery.<sup>(3)</sup> However, the recommendation was changed following the recognition of an association between erythromycin use during the first two weeks of life and subsequent infantile hypertrophic pyloric stenosis (IHPS)

The incidence of IHPS in infants treated with erythromycin during the first two weeks of life ranges from 27 to 32 cases per 1000 live births.<sup>(4, 5, 6)</sup> The baseline IHPS incidence rate reported in the general infant population ranges from 0.85 to 5 cases per 1000 live births, with a most recent estimate between 1 and 3 cases per 1000.<sup>(7)</sup> It is not clear whether IHPS is associated with the macrolide class of antibiotics or limited to erythromycin. Azithromycin may have a lower potential for IHPS, based on physicochemical differences that exist between azithromycin and erythromycin in the areas of gastrokinesis and acid catalysis.<sup>(8)</sup> From an ethical standpoint, a study using azithromycin to prevent CT conjunctivitis and pneumonia is justified because antibiotic prophylaxis was the standard of care until the association of erythromycin with IHPS was recognized. There is still a need to prevent conjunctivitis and pneumonia in infants exposed to CT at birth.

Azithromycin is labeled for use in infants six months of age and older. Off-label use of azithromycin in infants younger than six months of age occurs. However, no published controlled studies of azithromycin treatment for chlamydial pneumonia during the first six months of life were located in the English literature (1990-2003). In vitro, minimal inhibitory and minimal bactericidal concentrations of azithromycin have been reported to be similar to those of erythromycin against CT in vitro.

Differences between azithromycin and erythromycin metabolism may provide dosing regimen advantages of azithromycin for the infant. Based on a longer half-life, azithromycin would need to be given less frequently than erythromycin.

**Drug Indications:**

1. Oral azithromycin for the treatment of CT pneumonia in infant patients less than four months of age.
2. Oral azithromycin for the prevention of CT conjunctivitis and pneumonia in at-risk infants less than two weeks of age.

**Types of Studies and Study Objectives:**

1. Single Dose Pharmacokinetics (PK) Study:  
To characterize single dose oral azithromycin pharmacokinetics, safety and tolerability in patients with CT pneumonia or conjunctivitis at one or more potentially clinically relevant doses. The initial dose of azithromycin in this study will be guided by extrapolation from data of azithromycin use in older infants, published literature and current medical practice. PK information from patients with pneumonia will guide the starting dose for Study 2. PK information from patients with conjunctivitis will help to guide the starting dose(s) used in Studies 3 and 4.
2. Efficacy, Safety and PK Study:
  - a. To determine oral azithromycin efficacy for the treatment of chlamydial pneumonia in comparison to oral erythromycin.
  - b. To characterize the safety profile of oral azithromycin in the treatment of CT pneumonia.
  - c. To characterize oral azithromycin multiple-dose pharmacokinetics in patients with CT pneumonia.
3. Single dose PK Study:  
To characterize single-dose oral azithromycin PK, safety and tolerability in infants less than two weeks of age born to mothers with untreated or inadequately treated genital tract infection at one or more clinically relevant doses. Initial dose will be guided by results of Studies 1 and 2.
4. Efficacy, Safety and PK Study:
  - a. To determine oral azithromycin efficacy, in comparison to placebo, for the prevention of CT conjunctivitis and pneumonia, in infants less than two weeks of age.
  - b. To observe the incidence of IHPS following oral azithromycin use in infants less than two weeks of age, compared with placebo.
  - c. To determine individual incidence rates of CT conjunctivitis and pneumonia following azithromycin use or placebo, in infants less than two weeks of age, who were born to mothers with untreated or inadequately treated CT genital tract infection.

- d. To characterize a safety profile for oral azithromycin.
- e. To characterize azithromycin multiple-dose pharmacokinetics in infants less than two weeks of age.

Study 1 will be submitted to and assessed by the FDA in a timely manner, prior to proceeding with Study 2. Study 2 will be submitted to and assessed by the FDA prior to proceeding with studies 3 and 4. In particular, the adverse event profile observed in Studies 1 and 2 will play a primary role in deciding whether to proceed. The pharmacokinetic data from studies 1 and 2 will guide dosing in studies 3 and 4. Results from the single dose pharmacokinetic studies of azithromycin (Studies 1 and 3) will be used in planning Studies 2 and 4, respectively.

**Age group in which all studies will be performed:**

Studies 1 and 2: Patients will be less than four months of age at study entry.

Studies 3 and 4: Patients will be less than two weeks of age at study entry.

**Entry Criteria:**

Studies 1 and 2 will include male and female patients with physical, radiologic and bacteriologic and other laboratory findings consistent with a diagnosis of CT pneumonia with or without conjunctivitis. Study 1 will also include patients with physical and bacteriologic findings consistent with a diagnosis of CT conjunctivitis alone. Studies 3 and 4 will include male and female patients who were born to mothers with untreated or inadequately treated CT genital tract infection, and lack evidence of CT infection at the time of study entry. The protocol will specify additional criteria for study inclusion/exclusion, and should specifically address prior antibiotic use.

**Study Design:**

Criteria for withdrawal of individual patients from any study will be defined in the protocols for Studies 2 and 4. An independent Data Monitoring Committee (DMC) will be established for Studies 2 and 4. The study stopping rules used by the DMC will be specified in all protocols.

Studies 1, 2, 3, and 4: Studies that assess pharmacokinetics will utilize sparse sampling and a population PK approach to minimize blood loss to individual patients. Sparse blood samples should be obtained at defined intervals to avoid collection of samples at fixed times. Bioanalytical methods to determine azithromycin concentrations must be capable of using small blood volumes to minimize blood loss.

Study 2: This study will be multicenter, prospective, randomized, double-blind, parallel-arm, and active-controlled, to assess oral azithromycin non-inferiority to oral erythromycin for the treatment of CT pneumonia with or without conjunctivitis. The protocol will specify the criteria for the diagnosis of CT pneumonia as well as criteria for pneumonia cure. Multiple-dose pharmacokinetics will be assessed in a subset of patients. Rationale for study duration will be provided in the protocol, taking into account that CT pneumonia may occur in patients through three months of age, with or without prior history of CT conjunctivitis.

Study 4: This study will be a multicenter, prospective, randomized, double-blind, parallel- arm and placebo-controlled. The study will evaluate oral azithromycin effectiveness in the prevention of CT conjunctivitis and pneumonia in comparison to placebo. The protocol will specify criteria for the

diagnoses of CT conjunctivitis and pneumonia. Criteria for the definition of IHPS will be specified in the protocol. Multiple-dose pharmacokinetics will be assessed in a subset of patients in Study 4.

**Number of Patients:**

Studies (1, 2, 3, and 4): A sufficient number of patients to characterize single-dose and multiple-dose pharmacokinetics.

Study 2: A sufficient number of patients should be enrolled to have at least 80% power to demonstrate non-inferiority of azithromycin to erythromycin for the treatment CT pneumonia using a 2-sided 95% confidence interval and a pre-specified non-inferiority margin that has been justified and agreed upon by the FDA. The size of the margin should take into account historical evidence of the treatment effect of erythromycin relative to placebo for the treatment of CT pneumonia. Natural history studies show a spontaneous cure rate of 27.2% (three of 11 patients) with a corresponding 95% confidence interval (6.0%, 61%).<sup>(9)</sup> Assuming an 80% cure rate for erythromycin, the lower bound of the 2-sided 95% confidence interval of the treatment effect of erythromycin relative to placebo is approximately 20%. A non-inferiority margin of 10% should be used in order to preserve a fraction of the treatment effect.

Study 4: There are two co-primary endpoints and the number of patients enrolled should fulfill both of the following: (a) A sufficient number of patients should be enrolled to have at least 80% power to demonstrate superiority of azithromycin to placebo for prevention of CT conjunctivitis and pneumonia, using an alpha level=0.05. (b) A sufficient number of patients should be enrolled to have at least 80% power to demonstrate the non-inferiority of azithromycin to placebo in the incidence of IHPS using a 2-sided 95% confidence interval and a pre-specified non-inferiority margin that has been justified and agreed upon by the FDA. Based on these requirements for the IHPS endpoint, a sample size of approximately 290 evaluable patients per arm would provide at least 80% power to demonstrate the non-inferiority of azithromycin to placebo in the incidence of IHPS for up to a four-fold increase in the IHPS rate for the azithromycin group relative to placebo. The estimated placebo IHPS incidence rate is 0.19%, and the non-inferiority margin is 3%.<sup>(10)</sup> In addition, all parameter estimates used in the sample size calculation should pre-specified and justified in the protocol.

Consideration should be given to the fact that IHPS occurs predominantly in males, and is more frequent in Caucasian and Hispanic/Latino infants than African-American and Asian infants. Investigators are strongly encouraged to enrich the study population with respect to the risk of IHPS, while at the same time assuring adequate gender, ethnic and racial distribution to allow for labeling of azithromycin for all population groups.

The protocols for these studies will be discussed with the FDA and agreed upon prior to study initiation. All measurement estimates used in sample size calculation will be specified and justified in the protocol.

**Statistical information:**

These studies must have a pre-specified detailed statistical analysis plan appropriate for the study design and outcome measures. It will be discussed with the FDA and agreed upon prior to initiating studies. Demographic and safety data other than incidence of IHPS will be tabulated, and descriptive analysis of safety data will be provided. Descriptive statistics of the pharmacokinetic data must also be

provided and dose-response relationships and relationships between PK parameters and patient characteristics will also be explored.

**Assessment Parameters:**

**Pharmacokinetics:**

(All studies): The plasma clearance and volume of distribution of oral azithromycin will be calculated and to the extent possible other PK parameters such as the maximum plasma concentration ( $C_{max}$ ), time of  $C_{max}$  ( $T_{max}$ ), area under the plasma concentration-time curve from zero to the last quantifiable concentration ( $AUC_{0-t}$ ), the elimination rate constant ( $K_e$ ), terminal elimination half-life ( $t_{1/2}$ ), and AUC extrapolated to infinity ( $AUC_{0-\infty}$ ), should be determined. Adequate rationale for excluding any of the aforementioned PK parameters will be provided. If possible, the protein binding of azithromycin should be determined over the range of clinically relevant concentrations.

**Efficacy:**

Study 2: The protocol will specify a primary endpoint to comparatively evaluate the use of oral azithromycin and oral erythromycin in treatment of chlamydial pneumonia. This must include measures of bacteriologic and clinical cure. Secondary endpoints may include duration of time required for resolution of clinical and laboratory findings, need for hospitalization, and recurrence of chlamydial infection after initial resolution, and bacteriologic and clinical cure of conjunctivitis.

Study 4: The protocol will specify oral azithromycin effectiveness, compared with placebo, for the prevention of CT conjunctivitis and pneumonia as one of the co-primary endpoints. Criteria for diagnoses of CT conjunctivitis and pneumonia will be provided in the protocol, including clinical and bacteriologic measures. Incidence of IHPS will be evaluated as the second co-primary endpoint element. Criteria for the diagnosis of IHPS will be provided in the protocol. Secondary endpoints will include comparison of individual rates of CT conjunctivitis and pneumonia in relation to oral azithromycin or placebo administration.

**Drug –Specific Safety Concerns (all studies):**

1. It is unknown whether azithromycin has an adverse events profile similar to or different than that reported for erythromycin, with respect to infantile hypertrophic pyloric stenosis.
2. Colonization and infection with other bacterial (including macrolide-resistant organisms) and non-bacterial organisms (e.g. fungus) may occur with azithromycin treatment.
3. Macrolides have been associated with hearing loss at high doses. The potential for hearing loss with azithromycin treatment in this population will be assessed.

**Safety (all studies):**

Safety assessments will include occurrence of any adverse events (AEs), incidence of superinfections (particularly fungal infections), vital signs that include heart rate, blood pressure, respiratory rate, pulse oximetry, standard laboratory assessments of hematologic, liver and renal function, assessments of hearing, and growth (weight, length and head circumference). AEs will be followed to their resolution or stabilization. Nosocomial infection will be tracked by pathogen.

**Drug information:**

- ◆ Dosage form: approved age appropriate oral formulations of azithromycin and erythromycin

- ◆ Route of administration: oral
- ◆ Regimen: To be determined

Selection of doses for azithromycin in Study 1 will be guided by extrapolation of data from azithromycin use in older infants, published literature and/or current medical practice. Azithromycin doses chosen for Study 2 will be guided by the results of Study 1. For Studies 1 and 2, erythromycin dose will be based on current medical practice. Selection of azithromycin doses for Study 3 will be guided by the results of Studies 1 and 2. Azithromycin doses for Study 4 will be guided by the results of the first three studies.

**Labeling that may result from the studies:**

Appropriate sections of the label may be changed to incorporate the findings of the studies.

**Format of reports to be submitted:**

Full study reports not previously submitted to the Agency addressing the issues outlined in this request, with full analysis, assessment, and interpretation are required. Pharmacokinetic study reports will include analytical method and assay validation, individual drug concentration-time data and individual pharmacokinetic parameters (and pharmacodynamic data when available). In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

**Response to Written Request:**

As per the Best Pharmaceuticals for Children Act, Section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – COMPLETE RESPONSE TO WRITTEN REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR**

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**PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

### References

1. Rosenman MB et al. Oral erythromycin prophylaxis vs. watchful waiting in caring for newborns exposed to *Chlamydia trachomatis*. Arch Pediatr Adolesc Med 2003; 157:565-571.
2. Report of the Committee on Infectious Diseases, American Academy of Pediatrics, Twenty-Sixth Edition, 2003.
3. Report of the Committee on Infectious Diseases, American Academy of Pediatrics, Twenty-Fourth Edition, 1997.
4. Cooper WO et al. Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. Arch Pediatr Adolesc Med 2002; 156:647-650.
5. Mahon BE et al. Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. J Pediatr 2001; 139:380-384.
6. Honein MA et al. Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin. Lancet 1999; 354:2101-2105.
7. Personal Communication, Centers for Disease Control, May 2004.
8. Hauben M, Amsden GW. The association of erythromycin and infantile hypertrophic pyloric stenosis. Drug Safety 2002; 25(13): 929-942.
9. Beem MO et al. Treatment of chlamydial pneumonia of infancy. Pediatrics 1979; 63:198-203.
10. Schecter R et al. The epidemiology of infantile hypertrophic pyloric stenosis. Paediatr Perinat Epidemiol 1997; 11(4):407-427.