Dear CONTACT:

To obtain pediatric information on the use of intravenous azithromycin, the 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:
Respiratory tract colonization with *Ureaplasma urealyticum* may be a factor in the development of neonatal bronchopulmonary dysplasia (BPD). Although this has not been proven, macrolide antibiotics have been used to eradicate *U. urealyticum* colonization from the respiratory tract in this subpopulation. Literature suggests that macrolide antibiotics may also have an anti-inflammatory effect. The objective of these studies will be to investigate the safety and effectiveness of intravenous azithromycin for the prevention of BPD in preterm neonates colonized with *U. urealyticum.*
Azithromycin offers several potential advantages for treatment of *U. urealyticum*-colonized premature neonates. *In vitro* data indicate that *U. urealyticum* is susceptible to azithromycin. The intracellular accumulation of azithromycin and its tissue penetration are potential advantages for the treatment of intracellular pathogens. Azithromycin is likely to have fewer drug interactions than the other macrolides, since it is minimally metabolized and has a low potential to inhibit hepatic CYP 450 isozymes. However, there is minimal information about azithromycin dosing, efficacy, and safety in the neonatal period. Further, some macrolide antibiotics have been associated with adverse effects, such as pyloric stenosis and cardiac arrhythmias, and it is unknown whether azithromycin carries similar risk.

Types of Studies:
(1) Single Dose Pharmacokinetic (PK) Study:
• To characterize single dose intravenous (I.V.) azithromycin pharmacokinetics, safety and tolerability in mechanically ventilated preterm neonatal patients with *U. urealyticum* endotracheal colonization at one or more clinically relevant doses.
(2) Multiple-dose, Exposure Response Study(-ies):
• To assess the effect of two or more dose regimens of I.V. azithromycin on *U. urealyticum* colonization of the respiratory tract of preterm neonatal patients.
• To characterize multiple-dose PK and safety of I.V. azithromycin.
• To determine appropriate testing methods for documentation of *U. urealyticum* colonization and eradication.
• To explore potential for azithromycin clinical effectiveness.
(3) Efficacy and Safety Studies:
• Two studies that each assesses I.V azithromycin efficacy and safety for the prevention of BPD in mechanically ventilated preterm neonatal patients with *U. urealyticum* endotracheal colonization.
These studies will be performed in the above sequence and results of each study submitted to and assessed by FDA prior to proceeding with the next study(ies). Results from the single dose PK study would be used in planning the exposure-response study(ies). Similarly, results from the exposure response

study(ies) will be used, to the extent possible, for planning safety and efficacy studies.

Age group in which studies will be performed:

Studies will be performed in preterm neonatal patients <72 hours of age.

Entry criteria:

Preterm male and female patients <72 hours of age who are at least 23 weeks gestational age and 500 grams weight at time of birth will be eligible for enrollment in the studies. These patients will be endotracheally intubated, mechanically ventilated and have vascular access at the time of randomization. Patients must have documented *U. urealyticum* endotracheal colonization at the time of randomization.

Patients for whom a decision has been made to withdraw medical support, or in whom potentially lethal congenital defect(s) has been diagnosed by the medical team, are not eligible for study. Patients with central nervous system infections suspected to be due to *U. urealyticum* will be excluded. The protocol will specify additional criteria for study inclusion/exclusion, including when there has been antenatal maternal treatment with a macrolide or sulfa containing antibiotic.

Study design:

Criteria for withdrawal of individual patients from any study will be defined in the protocol. An independent Data Monitoring Committee (DMC) will be established for all exposure-response and safety and efficacy studies. The study stopping rules used by the DMC will be specified in all protocols.

Study Types 1 and 2: Studies that assess pharmacokinetics may use sparse sampling and population PK approach to minimize blood loss to individual patients. Bioanalytical methods to determine azithromycin concentrations must be capable of evaluating microliter sample volumes. Patients will be grouped by gestational age. A rationale will be provided for the grouping of patients by gestational age.

Appropriate testing methods for documentation of *U. urealyticum* colonization in the safety and efficacy trials will in part be determined from the exposure-response study(-ies). Study(ies) Type 2 will use both endotracheal culture and polymerase chain reaction (PCR) as methods for establishing respiratory tract colonization and the microbiological effect of azithromycin treatment. Additionally, Study(ies) Type 2 will evaluate the relationship between azithromycin dose and/or plasma exposure and microbiological eradication, and will explore potential for azithromycin clinical effectiveness.

Study Type 3: Two studies that assess efficacy and safety will be multicenter, randomized, double blind, and placebo controlled. There are numerous potential factors related to clinical management of sick preterm infants that may impact on the development of BPD (e.g. prenatal corticosteroids, postnatal corticosteroids, surfactant, type and mode of ventilation, inspired oxygen concentration (FiO2), fluid and electrolyte management and infant nutrition, vitamin A, congenital and nosocomial infections/pneumonia). The study will track and evaluate factors that may contribute to the development of BPD.

Patients will be stratified by gestational age in efficacy and safety studies. Other factors such as maternal chorioamnionitis and disease severity may be additionally considered. The rationale for patient stratification will be provided in protocols.

Number of patients:

Study Types 1 and 2: A sufficient number of patients to characterize single-dose and multiple dose pharmacokinetics will complete these studies. The protocol for these studies will be discussed with the FDA and agreed upon prior to initiation of the studies. Preterm neonates will be reasonably distributed by gender. The gestational age of these patients will reflect gestational age range of the efficacy and safety studies.
Study Type 3: Efficacy and safety studies will enroll a sufficient number of patients to ensure at least 80% statistical power to determine a treatment effect, at a 0.05 statistical significance level (two- tailed). All parameter estimates used in the sample size calculation will be specified and justified in the protocol.

Assessment Parameters:
Pharmacokinetics (Studies Type 1 and 2): The plasma clearance and volume of distribution of I.V. azithromycin will be calculated and 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 (Ke), terminal elimination half-life ($t_{1/2}$), and AUC extrapolated to infinity ($AUC_{0-\infty}$) will be determined to the extent possible. Adequate rationale for excluding any of the aforementioned PK parameters will be provided. The protein binding of azithromycin should be determined over the range of clinically relevant concentrations.
Pharmacodynamics (**Study(ies) Type 2):** Microbiologic persistence of *U. urealyticum* will be assessed by culture and PCR.
Efficacy (Studies Type 2 and 3): For Study(ies) Type 2, endpoints for efficacy will be explored. For powered efficacy and safety studies (Study Type 3), the protocol will specify a clinically meaningful primary endpoint to assess the treatment effect of azithromycin. Examples of such endpoints may include survival without severe BPD, survival without BPD, incidence of BPD, or incidence of severe BPD. A definition of BPD will be specified in the protocol. This protocol definition must include BPD diagnostic criteria and address how a patient's requirement for supplemental oxygen will be determined. Secondary endpoints will include overall mortality, incidence of co-morbidities of prematurity, number of days on the ventilator, number of days receiving oxygen supplementation, use of non-study antibiotics, and adverse events. Endpoints may also include the microbiological persistence of *Ureaplasma*.
Safety (Studies Types 1-3): Laboratory tests for safety must be performed on microliter serum samples. In addition, safety assessments will include occurrence of any adverse events (AEs), comorbidities of prematurity {e.g., necrotizing enterocolitis (NEC), sepsis, retinopathy of prematurity **(**ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), patent ductus arteriosus (PDA)}, incidence of superinfections (particularly fungal infections), vital signs that include heart rate (HR), blood pressure (BP), respiratory rate (RR), pulse oximetry, electrocardiogram (EKG) 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.
Long-term outcomes (Study Type 3): Assessments of growth, neurodevelopmental and pulmonary outcomes will be performed. These assessments may include, but are not limited to weight, length, head circumference, physical examination with neurologic

assessment, neurodevelopmental evaluation using a validated instrument, adverse events, hospitalization with emphasis on reactive airway disease and infection, medication history and use of oxygen. Provisions for these assessments may be included in the safety and efficacy protocols, or these assessments may be included in additional study protocols. At a minimum, long-term assessments will be performed through 24 months of the patient's chronological age.

Drug information:

- Dosage form: Approved intravenous formulation
- Route: Intravenous
- Regimen: To be determined

Selection of doses in the single-dose studies will be guided by literature or current medical practice.

Doses chosen for the subsequent trials will be guided by the results of preceding studies.

Drug specific safety concerns:

1. It is unknown whether azithromycin has an adverse events profile similar to that reported for other macrolide antibiotics. These include hypertrophic pyloric stenosis, and cardiac arrhythmias.
2. It is unknown whether there will be any adverse effects in this patient population related to the occurrence of phospholipidosis with azithromycin.
3. Colonization and infection with other bacterial (including macrolide-resistant organisms) and nonbacterial organisms (e.g., fungus) may occur with azithromycin treatment.
4. Macrolides have been associated with hearing loss at high doses. The potential for hearing loss with azithromycin treatment in this population will be assessed.

Statistical information:

These studies must have a pre-specified and detailed statistical analysis plan appropriate to the study design and outcome measures. It will be discussed with the FDA and agreed upon prior to initiating studies.

Demographic and safety data will be tabulated and descriptive analysis of safety data will be provided. Descriptive statistics of pharmacokinetic data must also be provided and dose-response relationships and relationships between PK parameters and patient characteristics will also be explored.

Labeling that may result from the Study(ies): 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 (including assay method validation information), assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and
racial minorities.

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 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 to 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.

If you have any questions, call Judit Milstein, Project Manager, at (301) 827-2125.

Sincerely,

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Mark Goldberger
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