Division Director Memorandum NDA 50-797/S-008

Application Number:	NDA 50-797
Supplement Number:	S-008
Submission Dates	October 19, 2007, and May 22, and September 15 and 19, 2008
Review Completion Date	October 7, 2008
Name	Azithromycin extended release powder for oral suspension
Trademark	Zmax™
Therapeutic Class	Macrolide antimicrobial
Applicant	Pfizer

Azithromycin was first approved in the US in 1991, and multiple dosage forms/formulations are approved for several anti-infective indications in adult and pediatric patients. Oral and intravenous formulations are labeled for treatment of community-acquired pneumonia. The oral formulation is also labeled for treatment of acute bacterial sinusitis (3-day course of treatment) and acute otitis media (1-, 3-, or 5-day).

Zmax™ is an azithromycin extended release (ER) formulation that was approved in 2004 for treatment of adults with mild to moderate community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS). Zmax™ is administered to adults in a single 2-gram dose of an oral suspension. The proposed pediatric indication is for the treatment of mild to moderate **(b) (4)** [redacted] in pediatric patients and uses a 2-gram bottle which is to be reconstituted to achieve a 27 mg/mL suspension. The proposed dosing regimen is a single, one day 60 mg/kg dose, which is equivalent to one milliliter (27 mg/mL) per pound of body weight up to a maximum of 2 grams of azithromycin suspension. The submission also included proposals for pediatric use statements for CAP.

Efficacy

For community acquired pneumonia, the efficacy of azithromycin ER in adults was demonstrated in non-inferiority studies of patients with mild-to-moderate CAP. The similar pathophysiology and expected response to treatment of mild-to-moderate CAP in adult and pediatric patients allows for extrapolation of adult efficacy in this indication to the pediatric population provided that there is adequate safety information. As noted below, adequate pediatric safety information has been provided in this submission (see below).

Safety
The safety profile of azithromycin is well established through prior submissions and agency reviews. The extended release formulation in the pediatric population was evaluated in 907 pediatric patients from 3 months to 12 years of age in this submission. These patients were given a single 60 mg/kg dose of azithromycin ER. The common adverse events include vomiting, diarrhea, loose stools, and abdominal pain. The safety findings in the pediatric population treated with azithromycin ER are consistent with those seen in pediatric patients receiving immediate release formulations of azithromycin. (See MOR dated August 13, 2007 and Clinical Team Leader Memorandum of September 28, 2007). The proposed pediatric dosage regimen employs a diluted solution (approximately 27 mg/mL) to minimize the incidence of vomiting in pediatric patients.

Pharmacology/Toxicology Review
No new Pharmacology/Toxicocology information was submitted. No additional Pharmacology/Toxicology information on azithromycin was considered needed for the proposed indications.

Chemistry/Manufacturing Controls Review
There are no proposed changes to the CMC section of the drug substance and drug product in this supplement. The content uniformity results indicated that adequate, aliquoted volumes of the drug product suspension can be administered to achieve appropriate dosage for patients less than 75 pounds in weight. The Environmental Assessment concluded that there was no significant impact.

Biopharmacology Review
The Biopharmacology Review concludes that the Clinical Pharmacology and Biophramaceutics information supports the proposed dose of 60 mg/kg in the treatment of (b) (4), CAP (b) (4) in pediatric patients.

The Biopharmacology Review also states that the selection of the dosage regimen for azithromycin SR is based on PK/PD relationships identified from animal models of infection that suggest a relationship between azithromycin efficacy and the ratio of the area under the serum concentration-time curve to the minimal inhibitory concentration (AUC/MIC) as well as observations that higher initial concentrations of the drug at the infection site may help prevent selection of less susceptible sub-populations of the pathogen(s). The dose and dosing regimen selected by the Applicant is consistent with the known relationship between dose-concentration-response. Pediatric pharmacokinetic data submitted by the Applicant support the proposed dose of 60 mg/kg (maximum dose of 2 g) in children ages (b) months to 16 years. The mean pharmacokinetic profile in pediatric patients given 60 mg/kg (up to a maximum of 2 g) azithromycin SR on an empty stomach was comparable to that observed in adults given 2 g azithromycin SR under fasted conditions. The most commonly observed adverse events in clinical studies were usually related to the gastrointestinal tract and consisted of diarrhea/loose stools, nausea, abdominal pain, headache, and vomiting. Since the proposed regimen is a single dose, the impact of vomiting and the necessity for a second dose or an alternate therapy if vomiting occurs are potential concerns. The relationship between the timing of vomiting and exposure to azithromycin was explored in the two pediatric studies, in a study comparing the tolerability of azithromycin SR following administration of two different concentrations of suspension, and in a pediatric pharmacokinetic study. In general, patients who

vomited within 5 minutes and were re-dosed and who vomited between 5 and 30 minutes and were not re-dosed appeared to have serum azithromycin concentrations comparable to non-vomiters, but the limited data in vomiters are not sufficient to support a (b) (4)

(b) (4)

Labeling
The labeling has been revised to include the treatment of pediatric patients (6 months of age and older) with community-acquired pneumonia, class warnings concerning mysasthenia gravis .

The revised labeling is listed below:

[redacted]

Conclusions

NDA 50-797, Supplement 8 supports the addition of the CAP indication for pediatric patients. The pediatric CAP has been added to the labeling. In addition, the Warnings section for exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome has been strengthened.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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Wiley Chambers
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