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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
50-784

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 50-784
Date: July 27, 2001
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Pfizer, Inc.

Reviewer name: Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.
Division name: Division of Anti-infective Drug Products
HFD #: 520
Review completion date: April 26, 2002

Drug: Trade name: Zithromax
Generic name: Azithromycin

This NDA contained no pharmacology or toxicology data. The sections of the label dealing with "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy" and "Animal Toxicology" have been reviewed. Only the "Animal Toxicology" section was in need of revision. This section now reads as follows (the sentences have been numbered for ease of locating the revisions suggested below).

ANIMAL TOXICOLOGY

1 Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. **2** It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which,

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4 Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. **5** Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 µg/mL (six times greater than the observed C_{max} of 0.216 µg/mL at the pediatric dose of 10 mg/kg). **6** Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 µg/mL (seven times greater than the observed same C_{max} and drug dose in the studied pediatric population). **7**

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Revisions are suggested to the 2nd and 7th sentences as described below (the new wording is underlined).

2 It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on the basis of mg/m^2, are approximately equal to the recommended adult human dose, and in rats treated at doses that are approximately one-sixth of the recommended adult human dose.

7 On a mg/m^2 basis, 30 mg/kg dose in the neonatal rat (135 mg/m^2) and 10 mg/kg dose in the neonatal dog (79 mg/m^2) are approximately 0.5 and 0.3 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg.

/S/

Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.
Pharmacologist/Toxicologist HFD-520

cc: list:
Original NDA 50-784
HFD-104
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/MO/A. Davidson
HFD-520/Micro/H. Silver
HFD-520/Chem/A. Yu
HFD-520/CSO/J. Milstein

Concurrence only:

HFD-520/TLPharm/T. Peters

HFD-520/DepDir/L. Gavrilovich

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/s/

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5/6/02 03:34:45 PM
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Terry Peters
5/14/02 07:30:13 AM
PHARMACOLOGIST

Lillian Gavrilovich
5/15/02 06:17:14 PM
MEDICAL OFFICER