CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-720/S-015

MEDICAL REVIEW

DIV F. 50-754

DEC 10 1999

Medical Officer's Review of Supplemental NDA's

NDA 50-542/S-017 Amoxil (amoxicillin) Chewable Tablets

NDA 50-754/S-002 Amoxil (amoxicillin) Tablets

NDA 50-760/S001 Amoxil (amoxicillin) for Oral Supension

NDA 50-761/S-001 (Amoxil) (amoxicillin) Chewable Tablets

Date of Submission: September 24, 1999

Applicant: SmithKline Beecham Pharmaceuticals
One Franklin Plaza
Philadelphia, PA 19101

Drug Product:
Proprietary Name: Amoxil®

APPEARS THIS WAY
ON ORIGINAL

Established Name: Amoxicillin

Route of Administration: Oral

How Supplied:
Tablets, 500 mg and 875 mg
Chewable Tablets, 125 mg, 200 mg, 250 mg, and 400 mg
Oral Suspension, 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL.
Pediatric Drops for Oral Suspension
15-mL bottle (50 mg/mL)
30-mL bottle (50 mg/mL)

Purpose of Submission:
These labeling supplements are submitted to revise the ADVERSE REACTIONS section of the labeling on the grounds of safety.

The revisions are as follows:
Gastrointestinal: "hemorrhagic colitis" added

Hypersensitivity Reactions: "serum sickness like reactions, exfoliative dermatitis, hypersensitivity vascultitis" added.

Liver: "ALT(SGPT), hepatic dysfunction including [redacted] and acute cytolytic hepatitis have been reported". Added

Hemic and Lymphatic Systems: "including hemolytic anemia" added

Central Nervous System: "Convulsions" added

Adverse Reaction Reports in Support of Labeling Changes

SmithKline Beecham searched their database for Amoxil reports from all sources (spontaneous, clinical, regulatory, and literature) of case reports containing the adverse event verbatim for the following coded terms (WHO Dictionary): moderate rise in SGPT, exfoliative dermatitis, convulsions, hepatic dysfunction (including cholestatic jaundice, hepatic cholestasis, acute cytolytic hepatitis), serum sickness, hypersensitivity vasculitis, hemorrhagic colitis, and hemolytic anemia. A summary of the findings follows:

Hemorrhagic colitis
There were 60 adverse reaction reports coded to hemorrhagic colitis. Of these, there were 53 reports with the verbatim term of hemorrhagic colitis. The remaining reports included the following verbatim terms: segmental hemorrhagic colitis (2), hemorrhagic enterocolitis (2), acute hemorrhagic enteritits (1), and pseudomembranous (ischemic) colitis (1) . In addition, there was one event of nonpseudomembranous colitis.

Serum sickness
There were 23 adverse reaction reports coded to serum sickness. Of these, there were 15 reports with the verbatim term of serum sickness. The remaining reports included: possible or suspected serum sickness (4), serum sickness – like reaction (1), and serum disease (1). In addition, there were three events of hives.

Exfoliative dermatitis
There were 17 adverse reaction reports coded to exfoliative dermatitis. The remaining reports included the following verbatim terms: cutaneous allergy (1), exanthema, allergic (1), necrotizing dermatitis (1), acute generalized pustular dermatitis (1) erythematous – papular dermtatitis (1), erythematous dermatitis (1) photosensitive dermatitis (1), Stevens – Johnson syndrome (1), allergic rash (1), erythematous rash (1), epidermal necrolysis (1), hematogenous contact-type dermatitis (1), and pruritus (1).

Liver enzymes
There were 27 adverse reaction reports coded to liver enzymes. The events included: elevated/increased SGPT(14), elevated hepatic or liver enzymes (7), transaminases increased (6).

Cholestatic Jaundice
There were 13 adverse reaction reports coded to cholestatic jaundice.

Hepatitis
There were 33 adverse reaction reports coded to hepatitis. These include the verbatim terms of cholestatic hepatitis, hepatic cytolysis, possible hepatitis, acute cytolytic hepatitis, granulomatous hepatitis, and hepatic insufficiency.

Hepatic cholestasis
There were 28 adverse reaction reports coded to hepatic cholestasis. Of these, there were 14 reports with the verbatim term of hepatitis cholestatic. The remaining reports included intraheptic cholestasis (5), cholestasis (6), mixed cholestatic – hepatocellular hepatitis (1), cholangitis (1), and hepatotoxicity (1).

Hemolytic anemia
There were 21 adverse reaction reports coded to hemolytic anemia. Of these, there were 15 reports with the verbatim term of hemolytic anemia. The remaining reports included the terms autoimmune hemolytic anemia (4), immune hemolytic anemia (1), and penicillin-induced hemolytic anemia (1).

Convulsions
There were 57 adverse reaction reports coded to convulsions. Of these, there were 22 reports with the verbatim term of convulsion including fever/grand mal convulsion, and 24 reports of seizures, including grand mal/absence seizure. The remaining reports included the verbatim terms: epilepsy aggravated (6), "fit/fits" (3), encephalopathy (1), and anaphylactic shock (1).

Conclusions:
The proposed labeling revisions are acceptable.

Recommendations:
It is recommended that these supplemental NDA's be approved. In addition, it is recommended that, at the next printing of the labeling , the word "anaphylactic " in the first sentence of the Warnings section be written in upper case.

/S/
Mercedes S. Albuerne, MD
Team Leader 10/28/99

CC: Orig NDA
NDA 50-542/S-017
NDA 50-754/S-002
NDA 50-760/S-001
NDA 50-761/S-001
HFD-520/DepDir/Gavrilovich
HFD-520/MOMakhene
HFD-520/PM/Cintron
HFD-520/Micro/King
HFD-520/Pharm/Seethaler
HFD-520/Chem/Yu

Concurrence Only:
HFD-520/DivDir/Chikami
HFD-520/TLMO/Albuerne

/S/ 12/10/99

APPEARS THIS WAY
ON ORIGINAL