MAY 16 2000

NDA 50-542/S-017
NDA 50-754/S-002
NDA 50-760/S-001
NDA 50-761/S-001

SmithKline Beecham
Attention: Dennen Stewart, Ph.D.
Regulatory Associate, Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7029

Dear Dr. Stewart:

Please refer to your supplemental new drug applications dated July 30, 1999, received August 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amoxil ®(amoxicillin) Chewable Tablets, NDA 50-542; Amoxil® (amoxicillin) Tablets, NDA 50-754; Amoxil® (amoxicillin) for Oral Suspension, NDA 50-760; Amoxil ® (amoxicillin) Chewable Tablets, NDA 50-761. We note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submission dated September 24, 1999.

These "Changes Being Effected" supplemental new drug applications provide for labeling changes to revise the ADVERSE REACTION section of the labeling.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted July 1999, AM; L18A 9416802). Accordingly, the supplemental applications are approved effective on the date of this letter.

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.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed, to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes; these submissions should be designated "FPL for approved supplements NDA 50-542/S-017, 50-754/S-002, 50-760/S-001, 50-761/S-001." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call CDR. Jose R. Cintron, USPHS, R.Ph., M.A., Project Manager, at (301) 827-2125.

Sincerely,

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ADVERSE REACTIONS
As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria. The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal: nausea, vomiting, diarrhea, and hemmorrhagic/pseudomembranous colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS** .)

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson Syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hypersensitivity vasculitis and urticaria have been reported.

NOTE: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver: A moderate rise in AST (SGOT) and/or ALT(SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis, and acute cytolytic hepatitis have been reported.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, and/or dizziness have been reported rarely.

Combination therapy with clarithromycin and lansoprazole
In clinical trials using combination therapy with amoxicillin plus clarithromycin and lansoprazole, and amoxicillin plus lansoprazole, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with amoxicillin, clarithromycin, or lansoprazole.

Triple therapy: amoxicillin/clarithromycin/lansoprazole
The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual therapy: amoxicillin/lansoprazole
The most frequently reported adverse events for patients who received amoxicillin t.i.d. plus lansoprazole t.i.d. dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin t.i.d. plus lansoprazole t.i.d. dual therapy than with lansoprazole alone.

For more information on adverse reactions with clarithromycin or lansoprazole, refer to their package inserts, **ADVERSE REACTIONS** .