CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-542/S-005, S-010, S-011

Trade Name: AMOXIL Capsules, Chewable Tablets, & Powder for Oral Suspension

Generic Name:(amoxicillin)

Sponsor: Smith Kline Beecham Pharmaceuticals

Approval Date: February 27, 1998

INDICATION: Provides for changes to the DESCRIPTION, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections of the labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50-542/S-005,010,011

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 50-542/S-005,010,011

APPROVAL LETTER

NDA 50-542/S-005, S-010, S-011

FEB 27 1998

SmithKline Beecham Pharmaceuticals
Attention: Ms. Sharon W. Shapowal
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pennsylvania 19101-7929

Dear Ms. Shapowal:

Please refer to your supplemental new drug applications dated January 17, 1990 (Supplement-005); November 11, 1994 (Supplement-010); and October 3, 1997, received October 6, 1997 (Supplement-011), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amoxil (amoxicillin) Capsules, Chewable Tablets, and Powder for Oral Suspension.

We note that this application is subject to exception provisions of Section 125(d)(2) of Title 1 of the FDA Modernization Act of 1997.

We also refer to our approvable letters to Supplement-005, dated June 8, 1993; and March 11, 1996; and Supplement-010, dated January 6, 1997.

In addition, we refer to your submissions to Supplement-005, dated February 10, 1995; and April 23, and July 30, 1997; and Supplement-010, dated April 23, and July 30, 1997.

Supplement-005 provides for changes to the **DESCRIPTION, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION,** and **HOW SUPPLIED** sections of the labeling.

Supplement-010 provides for changes to the **Microbiology** subsection of the **CLINICAL PHARMACOLOGY** section and the **REFERENCES** section of the labeling.

Supplement-011 provides for the addition of a new indication for Amoxil for use in combination with lansoprazole (with or without clarithromycin) in patients with duodenal ulcer (defined as an active ulcer or history of an ulcer within one year) to eradicate *Helicobacter pylori* and reduce the risk of duodenal ulcer recurrence. The User Fee Goal Date for this supplement is October 6, 1998.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft

labeling in the submissions dated February 26, 1998. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on February 26, 1998.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 50-542/S-005, S-010, S-011. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

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

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, Maryland 20852-9787

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, please contact Mr. Stephen T. Trostle, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

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

cc:

Original NDA (50-542/S-005, S-010, S-011)
HFD-520/Div. files
DISTRICT OFFICE
HFD-520/TL/MO/MAlbuerne MA 2/26/98
HFD-520/MO/MMakhene
HFD-520/TL/Micro/ASheldon AS 2/27/98
HFD-520/Micro/SAltaie S.S. Altaie 2/26/98
HFD-590/Micro/~~LUtrup~~ Shand
HFD-520/TL/Chem/DKatague DBK 2/27/98
HFD-520/Chem/AYu AYu 2/27/98
HFD-520/TL/Pharm/ROsterberg KS for REO 02/27/98
HFD-520/Pharm/KSeethaler KS 02/27/98
HFD-520/TL/Stat/DLin
HFD-880/TL/Biopharm/FPelsor 2/27/98
HFD-880/Biopharm/HSun
HFD-520/LGavrilovich (with labeling)
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-104/THassall (with labeling)
HFD-101/LCarter
HFD-830/ONDC Division Director
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling) ST 02/26/98
HFD-520/RHPM/STrostle/ft/stt/02/26/98 \n50542ap.005

For concurrence only:
HFD-520/C/PMS/JBona FVL 2-27-98 for JBona

APPROVAL (AP/NDA 50-542/S-005, S-010, S-011)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-542/S-005,010,011

FINAL PRINTED LABELING

APPROVED

AML13B

PRESCRIBING INFORMATION

9416646

AMOXIL®

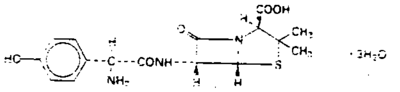
brand of

amoxicillin

capsules, powder for oral suspension and chewable tablets

DESCRIPTION

Amoxil (amoxicillin) is a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically it is D-(-)-α-amino-p-hydroxybenzyl penicillin trihydrate.



Amoxil capsules, tablets and powder for oral suspension are intended for oral administration.

Capsules: Each *Amoxil* capsule, with royal blue opaque cap and pink opaque body, contains 250 mg or 500 mg amoxicillin as the trihydrate. The cap and body of the 250 mg capsule is imprinted with the product name AMOXIL and 250; 500 mg—AMOXIL and 500. Inactive ingredients: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate and titanium dioxide.

Tablets: Each oval, pink, cherry-banana-peppermint-flavored tablet contains 125 mg or 250 mg amoxicillin as the trihydrate. The tablets are imprinted with the product name AMOXIL on one side and 125 or 250 on the other side. Inactive ingredients: citric acid, corn starch, FD&C Red No. 40, flavorings, glycine, mannitol, magnesium stearate, saccharin sodium, silica gel and sucrose.

Oral Suspension: Each 5 mL of reconstituted suspension contains 125 mg or 250 mg amoxicillin as the trihydrate.

Pediatric Drops for Oral Suspension: Each mL of reconstituted suspension contains 50 mg amoxicillin as the trihydrate

Amoxicillin trihydrate for oral suspension 125 mg/5 mL (reconstituted) is a strawberry-flavored pink suspension; the 250 mg/5 mL or 50 mg/mL is a bubble-gum-flavored pink suspension. Inactive ingredients: FD&C Red No. 3, flavorings, silica gel, sodium benzoate, sodium citrate, sucrose and xanthan gum.

ACTIONS

PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals. It is rapidly absorbed after oral administration. It diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein-bound. In blood serum, amoxicillin is approximately 20% protein-bound as compared to 60% for penicillin G.

Orally administered doses of 250 mg and 500 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 3.5 mcg/mL to 5.0 mcg/mL and 5.5 mcg/mL to 7.5 mcg/mL, respectively.

Orally administered doses of amoxicillin suspension 125 mg/5 mL and 250 mg/5 mL result in average peak blood levels 1 to 2 hours after administration in the range of 1.5 mcg/mL to 3.0 mcg/mL and 3.5 mcg/mL to 5.0 mcg/mL, respectively. Amoxicillin chewable tablets, 125 mg and 250 mg, produced blood levels similar to those achieved with the corresponding doses of amoxicillin oral suspensions.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Following a 1 gram dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

MICROBIOLOGY

Amoxil (amoxicillin) is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. *In vitro* studies have demonstrated the susceptibility of most strains of the following gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci and *Streptococcus faecalis*. It is active *in vitro* against many strains of *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Escherichia coli* and *Proteus mirabilis*. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Enterobacter* are resistant.

DISK SUSCEPTIBILITY TESTS: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with disks for testing susceptibility to ampicillin-class antibiotics. Interpretations correlate diameters of the disk test with MIC values for amoxicillin. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

*Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol. 45:493, 1966. Standardized Disc Susceptibility Test, Federal Register 37:20527-29, 1972.

Susceptibility testing for *Helicobacter pylori*:

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MIC's) and zone sizes have not been standardized, validated or approved for testing *H. pylori* microorganisms.

severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

USAGE IN PREGNANCY

Safety for use in pregnancy has not been established.

PRECAUTIONS

As with any potent drug, periodic assessment of renal, hepatic and hematopoietic function should be made during prolonged therapy. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Enterobacter*, *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

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 and diarrhea.

Hypersensitivity Reactions: Erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis 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 serum glutamic oxaloacetic transaminase (SGOT) has been noted, but the significance of this finding is unknown.

Hemic and Lymphatic Systems: 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, 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.

DOSAGE AND ADMINISTRATION

Infections of the ear, nose and throat due to streptococci, pneumococci, nonpenicillinase-producing staphylococci and *H. influenzae*;

Infections of the genitourinary tract due to *E. coli*, *Proteus mirabilis* and *Streptococcus faecalis*;

Infections of the skin and soft-tissues due to streptococci, susceptible staphylococci and *E. coli*:

USUAL DOSAGE:

Adults: 250 mg every 8 hours.

Children: 20 mg/kg/day in divided doses every 8 hours.

Children weighing 20 kg or more should be dosed according to the adult recommendations.

In severe infections or those caused by less susceptible organisms:

500 mg every 8 hours for adults and 40 mg/kg/day in divided doses every 8 hours for children may be needed.

Infections of the lower respiratory tract due to streptococci, pneumococci, nonpenicillinase-producing staphylococci and *H. influenzae*:

USUAL DOSAGE:

Adults: 500 mg every 8 hours.

Children: 40 mg/kg/day in divided doses every 8 hours.

Children weighing 20 kg or more should be dosed according to the adult recommendations.

Gonorrhea, acute uncomplicated ano-genital and urethral infections

antibiotics. Interpretations correlate diameters of the disk test with MIC values for amoxicillin. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

*Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol. 45:493, 1966. Standardized Disc Susceptibility Test. Federal Register 37:20527-29, 1972.

Susceptibility testing for *Helicobacter pylori*:

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MIC's) and zone sizes have not been standardized, validated or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used.

INDICATIONS

Amoxil (amoxicillin) is indicated in the treatment of infections due to susceptible strains of the following:

Gram-negative organisms–*H. influenzae, E. coli, P. mirabilis* and *N. gonorrhoeae*.

Gram-positive organisms–Streptococci (including *Streptococcus faecalis*), *D. pneumoniae* and nonpenicillinase-producing staphylococci.

Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin.

Indicated surgical procedures should be performed.

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

Triple therapy: Amoxil/*clarithromycin/lansoprazole*

Amoxil, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

Dual therapy: Amoxil/*lansoprazole*

Amoxil, in combination with lansoprazole delayed-release capsules as dual therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.** (See the clarithromycin package insert, MICROBIOLOGY.) Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH *AMOXIL*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AMOXIL* SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin, and may range in

staphylococci and *E. coli*:

USUAL DOSAGE:

Adults: 250 mg every 8 hours.
Children: 20 mg/kg/day in divided doses every 8 hours.
Children weighing 20 kg or more should be dosed according to the adult recommendations.

In severe infections or those caused by less susceptible organisms:

500 mg every 8 hours for adults and 40 mg/kg/day in divided doses every 8 hours for children may be needed.

Infections of the lower respiratory tract due to streptococci, pneumococci, nonpenicillinase-producing staphylococci and *H. influenzae*:

USUAL DOSAGE:

Adults: 500 mg every 8 hours.
Children: 40 mg/kg/day in divided doses every 8 hours.
Children weighing 20 kg or more should be dosed according to the adult recommendations.

Gonorrhea, acute uncomplicated ano-genital and urethral infections due to *N. gonorrhoeae* (males and females):

USUAL DOSAGE:

Adults: 3 grams as a single oral dose.
Prepubertal children: 50 mg/kg amoxicillin combined with 25 mg/kg probenecid as a single dose.

NOTE: SINCE PROBENECID IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS, THIS REGIMEN SHOULD NOT BE USED IN THESE CASES.

Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving amoxicillin, and monthly serological tests for a minimum of 4 months.

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

Triple therapy: Amoxil/*clarithromycin/lansoprazole*

The recommended adult oral dose is 1 gram Amoxil (amoxicillin), 500 mg clarithromycin and 30 mg lansoprazole, all given twice daily (q12h) for 14 days. (See INDICATIONS AND USAGE.)

Dual therapy: Amoxil/*lansoprazole*

The recommended adult oral dose is 1 gram *Amoxil* and 30 mg lansoprazole, each given three times daily (q8h) for 14 days. (See INDICATIONS AND USAGE.)

Please refer to clarithromycin and lansoprazole full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally impaired patients.

Larger doses may be required for stubborn or severe infections.

The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults.

It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

DOSAGE AND ADMINISTRATION OF PEDIATRIC DROPS

Usual dosage for all indications except infections of the lower respiratory tract:

Under 6 kg (13 lbs): 0.75 mL every 8 hours.
6 to 7 kg (13 to 15 lbs): 1.0 mL every 8 hours.
8 kg (16 to 18 lbs): 1.25 mL every 8 hours.

Infections of the lower respiratory tract:

Under 6 kg (13 lbs): 1.25 mL every 8 hours.
6 to 7 kg (13 to 15 lbs): 1.75 mL every 8 hours.
8 kg (16 to 18 lbs): 2.25 mL every 8 hours.

Children weighing more than 8 kg (18 lbs) should receive the appropriate dose of the Oral Suspension 125 mg or 250 mg/5 mL.

(continued on other side)

(continued from other side)

After reconstitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. Alternate means of administration are to add the required amount of suspension to formula, milk, fruit juice, water, ginger ale or cold drinks. These preparations should then be taken immediately. To be certain the child is receiving full dosage, such preparations should be consumed in entirety.

DIRECTIONS FOR MIXING ORAL SUSPENSION

Prepare suspension at time of dispensing as follows: Tap bottle until all powder flows freely. Add approximately 1/3 of the total amount of water for reconstitution (see table below) and shake vigorously to wet powder. Add remainder of the water and again shake vigorously.

125 mg/5 mL

Bottle Size	Amount of Water Required for Reconstitution
80 mL	62 mL
100 mL	78 mL
150 mL	116 mL

Each teaspoonful (5 mL) will contain 125 mg amoxicillin.

125 mg unit dose 5 mL

250 mg/5 mL

80 mL	59 mL
100 mL	74 mL
150 mL	111 mL

Each teaspoonful (5 mL) will contain 250 mg amoxicillin.

250 mg unit dose 5 mL

DIRECTIONS FOR MIXING PEDIATRIC DROPS

Prepare pediatric drops at time of dispensing as follows: Add the required amount of water (see table below) to the bottle and shake vigorously. Each mL of suspension will then contain amoxicillin trihydrate equivalent to 50 mg amoxicillin.

Bottle Size	Amount of Water Required for Reconstitution
15 mL	12 mL
30 mL	23 mL

NOTE: SHAKE BOTH ORAL SUSPENSION AND PEDIATRIC DROPS WELL BEFORE USING. Keep bottle tightly closed. Any unused portion of the reconstituted suspension must be discarded after 14 days. Refrigeration preferable, but not required.

HOW SUPPLIED

Amoxil (amoxicillin) **Capsules**. Each capsule contains 250 mg or 500 mg amoxicillin as the trihydrate.

250 mg Capsule

NDC 0029-6006-30 .....bottles of 100
NDC 0029-6006-32 .....bottles of 500

500 mg Capsule

NDC 0029-6007-30 .....bottles of 100
NDC 0029-6007-32 .....bottles of 500

Amoxil (amoxicillin) **Chewable Tablets**. Each cherry-banana-peppermint-flavored tablet contains 125 mg or 250 mg amoxicillin as the trihydrate.

125 mg Tablet

NDC 0029-6004-39 .....bottles of 60

250 mg Tablet

NDC 0029-6005-13 .....bottles of 30
NDC 0029-6005-30 .....bottles of 100

Amoxil (amoxicillin) **for Oral Suspension**.

125 mg/5 mL

NDC 0029-6008-21 .....80 mL bottle
NDC 0029-6008-23 .....100 mL bottle
NDC 0029-6008-22 .....150 mL bottle

250 mg/5 mL

NDC 0029-6009-21 .....80 mL bottle
NDC 0029-6009-23 .....100 mL bottle
NDC 0029-6009-22 .....150 mL bottle

Each 5 mL of reconstituted strawberry-flavored suspension contains 125 mg amoxicillin as the trihydrate.

Each 5 mL of reconstituted bubble-gum-flavored suspension contains 250 mg amoxicillin as the trihydrate.

NDC 0029-6008-18 .....125 mg unit dose bottle
NDC 0029-6009-18 .....250 mg unit dose bottle

Amoxil (amoxicillin) **Pediatric Drops for Oral Suspension**. Each mL of bubble-gum-flavored reconstituted suspension contains 50 mg amoxicillin as the trihydrate.

NDC 0029-6035-20 .....15 mL bottle
NDC 0029-6038-39 .....30 mL bottle

CLINICAL STUDIES

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or in combination with amoxicillin capsules as dual 14-day therapy, for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy: amoxicillin 1 gram b.i.d./clarithromycin 500 mg b.i.d./lansoprazole 30 mg b.i.d.

Dual therapy: amoxicillin 1 gram t.i.d./lansoprazole 30 mg t.i.d.

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

***H. pylori* Eradication Rates - Triple Therapy (amoxicillin/clarithromycin/lansoprazole) Percent of Patients Cured [95% Confidence Interval] (Number of Patients)**

Study	Triple Therapy Evaluable Analysis[1]	Triple Therapy Intent-to-Treat Analysis[2]

ogy and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

[2] Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.

[3] ($p<0.05$) versus lansoprazole alone.

[4] ($p<0.05$) versus lansoprazole alone or amoxicillin alone.

DATE OF ISSUANCE SEPT. 1997

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

9416646
AM:L13B

Printed in U.S.A.

amoxicillin as the trihydrate.

NDC 0029-6035-20 .....15 mL bottle
NDC 0029-6038-39 .....30 mL bottle

CLINICAL STUDIES

H. pylori eradication to reduce the risk of duodenal ulcer recurrence

Randomized, double-blind clinical studies performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) evaluated the efficacy of lansoprazole in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or in combination with amoxicillin capsules as dual 14-day therapy, for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy: amoxicillin 1 gram b.i.d./clarithromycin 500 mg b.i.d./lansoprazole 30 mg b.i.d.

Dual therapy: amoxicillin 1 gram t.i.d./lansoprazole 30 mg t.i.d.

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations. Dual therapy was shown to be more effective than both monotherapies. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

H. pylori Eradication Rates - Triple Therapy (amoxicillin/clarithromycin/lansoprazole) Percent of Patients Cured [95% Confidence Interval] (Number of Patients)

	Triple Therapy	Triple Therapy
Study	Evaluable Analysis[†]	Intent-to-Treat Analysis[‡]
Study 1	92[§] [80.0-97.7] (n=48)	86[§] [73.3-93.5] (n=55)
Study 2	86[‖] [75.7-93.6] (n=66)	83[§] [72.0-90.8] (n=70)

[†] Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest® (Delta West Ltd., Bentley, Australia), histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

[‡] Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.

[§] ($p<0.05$) versus lansoprazole/amoxicillin and lansoprazole/clarithromycin dual therapy.

[‖] ($p<0.05$) versus clarithromycin/amoxicillin dual therapy.

H. pylori Eradication Rates - Dual Therapy (amoxicillin/lansoprazole) Percent of Patients Cured [95% Confidence Interval] (Number of Patients)

	Dual Therapy	Dual Therapy
Study	Evaluable Analysis[†]	Intent-to-Treat Analysis[‡]
Study 1	77[§] [62.5-87.2] (n=51)	70[§] [56.8-81.2] (n=60)
Study 2	86[‖] [51.9-77.5] (n=58)	61[‖] [48.5-72.9] (n=67)

[†] Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histol-

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-542/S-005,010,011

MEDICAL REVIEW(S)

Medical Review of Supplement

NDA 50-542/S-011

OCT 28 1997

Date Submission Received: October 6, 1997

Applicant: SmithKline Beecham Pharmaceuticals

Drug Name: Amoxil® (amoxicillin) capsules, powder for oral suspension and chewable tablets

Category: β-Lactam

Date Review Started: October 15, 1997

Date Review Completed: October 20, 1997

Reviewer Note: The sponsor submitted this application as a "Special Supplement-Changes Being Effected." However, on October 7, 1997, the Division of Anti-Infective Drug Products responded in letter by stating, "Changes of the kind that you have proposed, in our opinion, are not the kind of changes permitted by regulation to be put into effect prior to approval of a supplement. An Approved supplement is required for the proposed changes; therefore, the supplement is being reviewed under 21 CFR 314.70(b)."

Purpose of Supplement:

The sponsor has submitted a labeling supplement to revise the labeling of Amoxil in accord with the approved labeling of PREVACID® (lansoprazole) Delayed-Release Capsules. The supplement adds a new therapeutic regimen to the Amoxil label and provides for the use of amoxicillin in combination with PREVACID (with or without clarithromycin) in patients with duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) to eradicate *Helicobacter pylori* and reduce the risk of duodenal ulcer recurrence.

Material Submitted:

1. Letter of Authorization from Tap Pharmaceuticals Inc. allowing FDA to make reference to data contained in NDA 20-406 approved on June 17, 1997, in support of the labeling supplement
2. Draft labeling of the Amoxil package insert

Comments: The applicant has added the following approved language from the PREVACID label to the Amoxil labeling:

In the Microbiology section, the following has been added:

"Susceptibility testing for *Helicobacter pylori:*

In vitro susceptibility testing methods and diagnostic products currently available for determining minimal inhibitory concentrations (MIC's) and zone sizes have not been standardized, validated or approved for testing *H. pylori* microorganisms. Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used."

Reviewer Comment: The entire heading for the paragraph beginning with "Susceptibility testing for... " should be italicized as it is in the PREVACID labeling. Also, the word "minimal" should be changed to "minimum."

In the INDICATIONS section, the following has been added:

Reviewer Comment: The headings for each of the above paragraphs should not be italicized.

In the DOSAGE AND ADMINISTRATION section, the following has been added:

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Reviewer Comment: These changes are acceptable.

Recommendations

This supplemental application should be approved provided the changes recommended above are made by the sponsor.

/S/

Luigi S. Girardi, M.D.

cc: Original NDA

HFD-520 files
HFD-590 files
HFD-520/PM/STrostle
HFD-520/TL/MAlbuerne 10/22/97
HFD-520/MO/LGirardi 10/22/97
HFD-590/MO/RHopkins
HFD-590/Micro/LUtrup
HFD-520/CPMS/JBona
HFD-590/Div.Dir./MGoldberger
HFD-520/Act.Div.Dir./GChikami
10/28/97