CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-725 / S-017

Trade Name: Augmentin

Generic Name: (amoxicillin / clavulanate potassium)

Sponsor: GlaxoSmithKline

Approval Date: May 12, 2003

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APPLICATION NUMBER:

50-725 / S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-725 / S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-575/S-032
NDA 50-597/S-039
NDA 50-725/S-017
NDA 50-726/S-014

GlaxoSmithKline
Attention: Dennen Stewart, Ph.D.
Assistant Director, U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pennsylvania 19101-7929

Dear Dr. Stewart:

Please refer to your supplemental new drug applications dated February 15, 2002, received February 19, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Augmentin® (amoxicillin/clavulanate potassium) 125 mg/5 mL and 250 mg/5 mL Powder for Oral Suspension (NDA 50-575), Augmentin® (amoxicillin/clavulanate potassium) 125-mg 250-mg Chewable Tablets (NDA 50-597), Augmentin® (amoxicillin/clavulanate potassium) 200 mg/5 mL and 400 mg/5mL Powder for Oral suspension (NDA 50-725), and Augmentin® (amoxicillin/clavulanate potassium) 200-mg and 400-mg Chewable Tablets (NDA 50-726). 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 May 8, 2003.

These supplemental new drug applications propose revisions to the **PRECAUTIONS, ADVERSE REACTIONS**, and **OVERDOSAGE** sections of the label on the basis of safety.

We have completed the review of these supplemental applications, as amended, 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 agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the Guidance for Industry titled "Providing Regulatory Submissions in Electronic Format – NDA". Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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, these submissions should be designated "FPL for approved supplement NDA 50-575/S-032, NDA 50-597/S-039, NDA 50-725/S-017, and NDA 50-726/S-014." 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 insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter) is 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, MD 20857

Please submit one market package of the drug product when it is available.

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 Susmita Samanta, M.D., Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth
5/12/03 03:19:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-725 / S-017

APPROVED LABELING

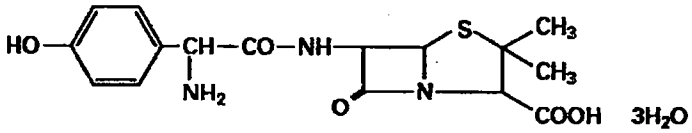
AG:AL9
PRESCRIBING INFORMATION

AUGMENTIN®

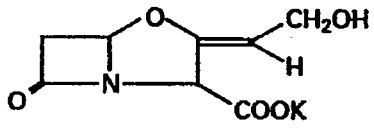
amoxicillin/clavulanate potassium
Tablets

DESCRIPTION

Augmentin is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ and the molecular weight is 419.46. Chemically, amoxicillin is (*2S,5R,6R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate and may be represented structurally as:



Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$ and the molecular weight is 237.25. Chemically clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate, and may be represented structurally as:



Inactive Ingredients: Colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate and titanium dioxide.

Each *Augmentin* tablet contains 0.63 mEq potassium.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of *Augmentin*. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While *Augmentin* can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In one study, the relative bioavailability of clavulanate was reduced when *Augmentin* was dosed at 30 and 150 minutes after the start of a high fat breakfast. The safety and efficacy of *Augmentin* have been established in clinical trials where *Augmentin* was taken without regard to meals.

Mean* amoxicillin and clavulanate potassium pharmacokinetic parameters are shown in the table below:

Dose† and regimen	AUC_{0-24} (µg.hr/mL)		C_{max} (µg/mL)	
amoxicillin/ clavulanate potassium	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)	amoxicillin (±S.D.)	clavulanate potassium (±S.D.)
250/125 mg q8h	26.7 ± 4.56	12.6 ± 3.25	3.3 ± 1.12	1.5 ± 0.70
500/125 mg q12h	33.4 ± 6.76	8.6 ± 1.95	6.5 ± 1.41	1.8 ± 0.61
500/125 mg q8h	53.4 ± 8.87	15.7 ± 3.86	7.2 ± 2.26	2.4 ± 0.83
875/125 mg q12h	53.5 ± 12.31	10.2 ± 3.04	11.6 ± 2.78	2.2 ± 0.99

* Mean values of 14 normal volunteers (n=15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.

† Administered at the start of a light meal.

Amoxicillin serum concentrations achieved with *Augmentin* are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half-life of amoxicillin after the oral administration of *Augmentin* is 1.3 hours and that of clavulanic acid is 1.0 hour.

Approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single *Augmentin* 250 mg or 500 mg tablet.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component in *Augmentin* is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

Microbiology: Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and, therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in *Augmentin* protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, *Augmentin* possesses the properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND

USAGE section.

GRAM-POSITIVE AEROBES
Staphylococcus aureus (β-lactamase and non-β-lactamase producing)‡
‡ Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

GRAM-NEGATIVE AEROBES
Enterobacter species (Although most strains of *Enterobacter* species are resistant *in vitro*, clinical efficacy has been demonstrated with *Augmentin* in urinary tract infections caused by these organisms.)
Escherichia coli (β-lactamase and non-β-lactamase producing)
Haemophilus influenzae (β-lactamase and non-β-lactamase producing)
Klebsiella species (All known strains are β-lactamase producing.)
Moraxella catarrhalis (β-lactamase and non-β-lactamase producing)

The following *in vitro* data are available, **but their clinical significance is unknown**.

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 0.5 μg/mL or less against most (≥90%) strains of *Streptococcus pneumoniae*§; MICs of 0.06 μg/mL or less against most (≥90%) strains of *Neisseria gonorrhoeae*; MICs of 4 μg/mL or less against most (≥90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 μg/mL or less against most (≥90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.
§ Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin.

GRAM-POSITIVE AEROBES
Enterococcus faecalis‖
Staphylococcus epidermidis (β-lactamase and non-β-lactamase producing)
Staphylococcus saprophyticus (β-lactamase and non-β-lactamase producing)
Streptococcus pneumoniae‖¶
Streptococcus pyogenes‖¶
viridans group *Streptococcus*‖¶

GRAM-NEGATIVE AEROBES
Eikenella corrodens (β-lactamase and non-β-lactamase producing)
Neisseria gonorrhoeae‖ (β-lactamase and non-β-lactamase producing)
Proteus mirabilis‖ (β-lactamase and non-β-lactamase producing)

ANAEROBIC BACTERIA
Bacteroides species, including *Bacteroides fragilis* (β-lactamase and non-β-lactamase producing)
Fusobacterium species (β-lactamase and non-β-lactamase producing)
Peptostreptococcus species¶
‖ Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.

¶ These are non-β-lactamase-producing organisms and, therefore, are susceptible to amoxicillin alone.

SUSCEPTIBILITY TESTING

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the following criteria:
RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For gram-negative enteric aerobes:

MIC (µg/mL)	Interpretation
≤ 8/4	Susceptible (S)
16/8	Intermediate (I)
≥ 32/16	Resistant (R)

For *Staphylococcus*** and *Haemophilus* species:

MIC (µg/mL)	Interpretation
≤ 4/2	Susceptible (S)
≥ 8/4	Resistant (R)

** Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

For *Streptococcus pneumoniae*: Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used:

MIC (µg/mL)	Interpretation
≤ 0.5/0.25	Susceptible (S)
1/0.5	Intermediate (I)
≥ 2/1	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms

to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)[††]
Escherichia coli ATCC 25922	2 to 8
Escherichia coli ATCC 35218	4 to 16
Enterococcus faecalis ATCC 29212	0.25 to 1.0
Haemophilus influenzae ATCC 49247	2 to 16
Staphylococcus aureus ATCC 29213	0.12 to 0.5
Streptococcus pneumoniae ATCC 49619	0.03 to 0.12

[††] Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg of amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 µg amoxicillin/clavulanate acid (20 µg amoxicillin plus 10 µg clavulanate potassium) disk should be interpreted according to the following criteria:

RECOMMENDED RANGES FOR AMOXICILLIN/CLAVULANIC ACID SUSCEPTIBILITY TESTING

For *Staphylococcus*[‡‡] species and *H. influenzae*[a]:

Zone Diameter (mm)	Interpretation
≥ 20	Susceptible (S)
≤ 19	Resistant (R)

For other organisms except *S. pneumoniae*[b] and *N. gonorrhoeae*[c]:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 to 17	Intermediate (I)
≤ 13	Resistant (R)

[‡‡] Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

[a] A broth microdilution method should be used for testing *H. influenzae*. Beta-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.

[b] Susceptibility of *S. pneumoniae* should be determined using a 1 µg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin/clavulanic acid. An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

[c] A broth microdilution method should be used for testing *N. gonorrhoeae* and interpreted according to penicillin breakpoints.

Interpretation should be as stated above for results using dilution techniques. Interpretation

involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 µg amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	19 to 25
Escherichia coli ATCC 35218	18 to 22
Staphylococcus aureus ATCC 25923	28 to 36

INDICATIONS AND USAGE

Augmentin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections–caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Otitis Media–caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Sinusitis–caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Skin and Skin Structure Infections–caused by β-lactamase-producing strains of *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella* spp.

Urinary Tract Infections–caused by β-lactamase-producing strains of *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin*. (See Microbiology subsection.)

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.
Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

CONTRAINDICATIONS

Augmentin is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of *Augmentin*-associated cholestatic

jaundice/hepatic dysfunction.

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. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE 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 *Augmentin*, and has ranged in 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 one primary cause of "antibiotic associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate 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 *Clostridium difficile* colitis.

Augmentin should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of *Augmentin* is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS–*Liver*.)

PRECAUTIONS

General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind

during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

In common with other broad-spectrum antibiotics, *Augmentin* may reduce the efficacy of oral contraceptives.

Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis: The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Impairment of Fertility: Augmentin at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m^2/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic effects. Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m^2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the

uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with *Augmentin* may be associated with an increased risk of necrotizing enterocolitis in neonates.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

ADVERSE REACTIONS

Augmentin is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthemous pustulosis and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely.

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. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. There have been reports of increased prothrombin time in patients receiving *Augmentin* and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

OVERDOSAGE

Following overdosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients.

In the case of overdosage, discontinue *Augmentin*, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 pediatric patients at a poison center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.[3]

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin. Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate. Both amoxicillin and clavulanate are removed from the circulation by hemodialysis. (See DOSAGE AND ADMINISTRATION for recommended dosing for patients with impaired renal function.)

DOSAGE AND ADMINISTRATION

Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.

Dosage:

Adults: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)

Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.

Administration: *Augmentin* may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal.

HOW SUPPLIED

***AUGMENTIN* 250 MG TABLETS:** Each white oval filmcoated tablet, debossed with AUGMENTIN on 1 side and 250/125 on the other side, contains 250 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0029-6075-27 ..... bottles of 30
NDC 0029-6075-31 ..... Unit Dose (10x10) 100 tablets

***AUGMENTIN* 500 MG TABLETS:** Each white oval filmcoated tablet, debossed with AUGMENTIN on 1 side and 500/125 on the other side, contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0029-6080-12 ..... bottles of 20
NDC 0029-6080-31 ..... Unit Dose (10x10) 100 tablets

***AUGMENTIN* 875 MG TABLETS:** Each scored white capsule-shaped tablet, debossed with AUGMENTIN 875 on 1 side and scored on the other side, contains 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

NDC 0029-6086-12 ..... bottles of 20
NDC 0029-6086-21 ..... Unit Dose (10x10) 100 tablets

***AUGMENTIN* is also supplied as:**

AUGMENTIN 125 MG/5 ML (125 mg amoxicillin/31.25 mg clavulanic acid) FOR ORAL SUSPENSION:

NDC 0029-6085-39 ..... 75 mL bottle
NDC 0029-6085-23 ..... 100 mL bottle
NDC 0029-6085-22 ..... 150 mL bottle

AUGMENTIN 200 MG/5 ML (200 mg amoxicillin/28.5 mg clavulanic acid) FOR ORAL SUSPENSION:

NDC 0029-6087-29 ..... 50 mL bottle
NDC 0029-6087-39 ..... 75 mL bottle
NDC 0029-6087-51 ..... 100 mL bottle

AUGMENTIN 250 MG/5 ML (250 mg amoxicillin/62.5 mg clavulanic acid) FOR ORAL SUSPENSION:

NDC 0029-6090-39 ..... 75 mL bottle

NDC 0029-6090-23 ..... 100 mL bottle
NDC 0029-6090-22 ..... 150 mL bottle

AUGMENTIN 400 MG/5 ML (400 mg amoxicillin/57 mg clavulanic acid) FOR ORAL SUSPENSION:
NDC 0029-6092-29 ..... 50 mL bottle
NDC 0029-6092-39 ..... 75 mL bottle
NDC 0029-6092-51 ..... 100 mL bottle

AUGMENTIN 125 MG (125 mg amoxicillin/31.25 mg clavulanic acid) CHEWABLE TABLETS:
NDC 0029-6073-47 ..... carton of 30 (5x6) tablets

AUGMENTIN 200 MG (200 mg amoxicillin/28.5 mg clavulanic acid) CHEWABLE TABLETS:
NDC 0029-6071-12 ..... carton of 20 tablets

AUGMENTIN 250 MG (250 mg amoxicillin/62.5 mg clavulanic acid) CHEWABLE TABLETS:
NDC 0029-6074-47 ..... carton of 30 (5x6) tablets

AUGMENTIN 400 MG (400 mg amoxicillin/57.0 mg clavulanic acid) CHEWABLE TABLETS:
NDC 0029-6072-12 ..... carton of 20 tablets

Store tablets and dry powder at or below 25°C (77°F). Dispense in original container.

CLINICAL STUDIES

Data from two pivotal studies in 1,191 patients treated for either lower respiratory tract infections or complicated urinary tract infections compared a regimen of 875 mg *Augmentin* tablets q12h to 500 mg *Augmentin* tablets dosed q8h (584 and 607 patients, respectively). Comparable efficacy was demonstrated between the q12h and q8h dosing regimens. There was no significant difference in the percentage of adverse events in each group. The most frequently reported adverse event was diarrhea; incidence rates were similar for the 875 mg q12h and 500 mg q8h dosing regimens (14.9% and 14.3%, respectively). However, there was a statistically significant difference ($p<0.05$) in rates of severe diarrhea or withdrawals with diarrhea between the regimens: 1.0% for 875 mg q12h dosing versus 2.5% for the 500 mg q8h dosing.

In one of these pivotal studies, 629 patients with either pyelonephritis or a complicated urinary tract infection (i.e., patients with abnormalities of the urinary tract that predispose to relapse of bacteriuria following eradication) were randomized to receive either 875 mg *Augmentin* tablets q12h or 500 mg *Augmentin* tablets q8h in the following distribution:

	875 mg q12h	500 mg q8h
Pyelonephritis	173 patients	188 patients
Complicated UTI	135 patients	133 patients
Total patients	308	321

The number of bacteriologically evaluable patients was comparable between the two dosing regimens. *Augmentin* produced comparable bacteriological success rates in patients assessed 2 to 4 days immediately following end of therapy. The bacteriologic efficacy rates were comparable at one of the follow-up visits (5 to 9 days post-therapy) and at a late post-therapy visit (in the majority of cases, this was 2 to 4 weeks post-therapy), as seen in the table below:

	875 mg q12h	500 mg q8h

2 to 4 days	81%, n=58	80%, n=54
5 to 9 days	58.5%, n=41	51.9%, n=52
2 to 4 weeks	52.5%, n=101	54.8%, n=104

As noted before, though there was no significant difference in the percentage of adverse events in each group, there was a statistically significant difference in rates of severe diarrhea or withdrawals with diarrhea between the regimens.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. NCCLS, Villanova, PA, December 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24. NCCLS, Villanova, PA, December 1993.
3. Swanson-Biearman B, Dean BS, Lopez G, Krenzelok EP. The effects of penicillin and cephalosporin ingestions in children less than six years of age. *Vet Hum Toxicol* 1988;30:66-67.

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Rx only

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

AG:AL9

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-725 / S-017

MEDICAL REVIEW

Medical Officer's Review of Labeling Supplement

1.0 Identification: NDA 50-575/S- 032: AUGMENTIN® (amoxicillin/clavulanate potassium)250 mg/5mL and 125 mg/5 mL powder for oral suspension

NDA 50-597/S-039: AUGMENTIN® (amoxicillin/clavulanate potassium) 125 mg and 250 mg chewable tablets

N[redacted]UGMENTIN® (amoxicillin/clavulanate potassium) 875 mg oral tablets

NDA 50-564/S-043: AUGMENTIN® (amoxicillin/clavulanate potassium) 250 mg and 500 mg oral tablets

NDA 50-725/S-017: AUGMENTIN® (amoxicillin/clavulanate potassium) 200 mg/5mL and 400 mg/5mL powder for oral suspension

NDA 50-726/S-014: AUGMENTIN® (amoxicillin/clavulanate potassium) 200 mg and 400 mg chewable tablets

NDA 50-755/S-003: AUGMENTIN ES-600™(amoxicillin/clavulanate potassium) 600 mg/5mL for oral suspension

1.1 Applicant Information

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101 -7929
Contact Person: Deneen Stewart, Ph.D.
Assistant Director
U.S. Regulatory Affairs
Tel. (215) 751-6318

1.2 Submission/Review Dates

Date of submission for NDAs 50-575/S-032, 50-597/S-039, 50-725/S-017, and 50-726/S-014: February 15, 2002.
Date of submission for NDA 50-720/S-015 and NDA 50-564/S-043: February 19, 2002
Date of submission for NDA 50-755/S-003: April 5, 2002
Date assigned to current reviewer: March 15, 2002 and April 15, 2002
Date of 1st draft review completed: July 22, 2002
Date of final review completed: April 1, 2003

1.3 Drug Identification

Generic Drug Name: Amoxicillin trihydrate/clavulanic acid
Trade Name: AUGMENTIN®; AUGMENTIN ES-600™
Dosage Form and Route of Administration: tablets and suspension for oral administration
Category: semisynthetic penicillin (analog of ampicillin), and beta-lactamase inhibitor, combination

2.0 Purpose of Supplement

This supplement is submitted in accordance with 21 CFR 314.70 (c)(2)(i) to revise the [redacted] and [redacted] ctions of the label for Augmentin on the grounds of safety.

3.0 Submitted materials

Four volumes (paper) for NDAs 50-575/S-032, 50-597/S-039, 50-725/S-017, and 50-726/S-014 were submitted containing the following sections: cover letter dated February 15, 2002; completed form FDA 356h; and completed form FDA 3397. One volume (paper) each for NDA 50-720/S-015 and NDA 50-564/S-043 containing a cover letter dated February 19, 2002, completed Form FDA 356h; and completed form FDA 3397 were submitted. One volume (paper) for NDA 50-755/S-003 containing a cover letter dated April 5, 2002; completed form FDA 356h; and completed form FDA 3397 were also submitted.

Electronic submission consisted of the following contents: cover letter dated February 15, 2002; completed form FDA 356h; confidentiality statement; completed form FDA 3397 (User Fee Form); [redacted] in the ADVERSE REACTIONS section; [redacted] and final printed labeling.

MO COMMENT:

The review of the four labeling supplements, Changes Being Effected (NDA 50-597/S-039; NDA 50-575/S-032; NDA 50-725/S-017; and NDA 50-726/S-014) is integrated since the applicant's proposed labeling revisions for the current insert are identical and apply to these four applications. The review of the two supplements (NDA 50-720/S-015 and NDA 50-564/S-