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

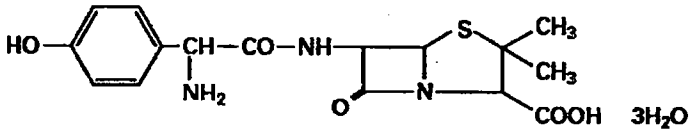
AG:AL9
PRESCRIBING INFORMATION

AUGMENTIN®

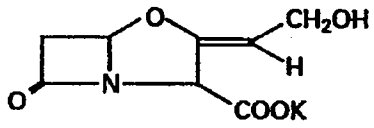
amoxicillin/clavulanate potassium
Tablets

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.

DATE OF ISSUANCE JAN. 2002

Rx only

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

AG:AL9

Printed in U.S.A.

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

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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-

043) are also integrated but only addressed the proposed revisions on necrotizing enterocolitis (NEC) in neonates, acute generalized exanthematous pustulosis (AGEP) and Overdosage. The last supplement NDA 50-755/S-003 (AUGMENTIN ES-600™ (amoxicillin/clavulanate potassium) 600 mg/5mL for oral suspension is also included in this review since the applicant's proposed revision addresses NEC in neonates. The differences between the seven applications are in the dose and dosage form.

4.0 Review of Data in Support of Changes Being Effected

The data supporting the proposed changes in the PRECAUTIONS, ADVERSE EVENTS, and OVERDOSAGE sections of Augmentin label were collected from the SmithKline Beecham (SB) database of AE reports from clinical trials, post marketing surveillance, spontaneous, literature and regulatory sources.

A. Supporting Information for the Labeling Changes of Necrotizing Enterocolitis in Neonates

According to the applicant, the primary sources of information used to address the issue of necrotizing enterocolitis (NEC) in neonates were the SmithKline Beecham (SB) Worldwide Clinical Safety Database and the medical literature. The database was searched on March 27, 2001 for all reports of patients who had received Augmentin or amoxicillin and had experienced AEs that had coded to one or more of the following WHO preferred terms: ulcerative colitis; gastric hemorrhage; intestinal gangrene; intestinal ulceration; melena; intestinal perforation; hemorrhagic colitis; intestinal necrosis; gastrointestinal mucosal necrosis general and intestinal ischemia. The dataset was then manually searched for all cases of NEC in neonates (1 to 28 days of age). A second search was performed for all cases involving the use of Augmentin in the treatment of neonates. The general AE profile was reviewed for this patient population.

The medical literature was searched for articles in which NEC in neonates associated with Augmentin and penicillins was discussed. The following medical information databases were used in this search: SB's in-house literature database (SB Line), ADIS Newsletters, Medline, Embase, Biosis, Scisearch and Derwent Drug Files. In addition to the literature articles, general textbooks including The Textbook of Gastroenterology, Textbook of Pediatrics and the Textbook of Neonatology were also used in the search.

Results

Information from the SB Clinical Safety Database

Two cases of NEC were retrieved from the search for Augmentin (Case # 1989900379-1, and Case #1989901945-1). No cases of NEC were retrieved from the search for amoxicillin. According to the applicant, both cases were very poorly documented which made the assessment difficult. Case # 1989900379-1 was a literature report from the Proceedings of the European Society of Pediatric Infectious in Athens. The applicant was unable to retrieve this article from the British Library.

MO Comment: ***The reviewer obtained a copy of the abstract for the cited case above (#1989900379-1) from the European Society of Pediatric Infectious Diseases. In this study (Augmentin in Neonatal Infections) of 33 neonates in France, one neonate developed NEC after ten days of Augmentin-aminoglycoside therapy. Augmentin was administered at 100 mg/kg/d intravenously. There is no mention of the dose and name of the aminoglycoside. No further details of this case were stated in the abstract.***

Brief narratives of the two cases cited above are as follows:

- Case #1989900379-1: This is a newborn infant (between day 0 and day 4 of life) who received intravenous Augmentin for 10 days for a suspected infection. After 10 days of therapy, the infant developed necrotizing enterocolitis. The sex of the infant is unknown in the report. The outcome is unknown. (Note: No other information was provided in the report by the applicant since the literature article was not retrieved.)

- Case #1989901945-1: This is an infant born at 36 weeks gestation and operated on at age 36 hours for a midgut volvulus and resection of jejunum. The patient had a second operation some time later for ischemic atresia and lost 200 ml of blood during the operation. The infant received a blood transfusion and was treated prophylactically with 90 mg Augmentin (30mg/kg) as a single dose post-operatively. A further six doses of Augmentin were administered intravenously post-operatively at eight hourly intervals. Approximately one month later, the child developed necrotizing enterocolitis and was re-operated upon for complete removal of the bowel. The infant died post-operatively. The report stated that the cause of death was unknown. According to the applicant, the infant developed intestinal ischemia, which is regarded as one of the predisposing risk factors for NEC.

A review of the general AE profile for neonates receiving treatment with Augmentin was also performed according to the applicant. A total of 14 AEs have been reported to the applicant in neonates. The applicant reported no apparent safety signals from this dataset. The most frequently reported AEs were conditions that may have been related to underlying infections (e.g., sepsis, pneumonia). Note: Please see applicant's table below for the total 14 adverse events.

Table 1: General Adverse Events Profile in Neonates

Case Number	Adverse Event (Verbatim)	Age/Sex of Patient	Dose/Route of Administration	Indication	Outcome
1986901011-1	Congenital abnormality	Newborn	Exposure in utero	N/A	N/A
1991900092-1	Cardiac failure, cholestasis & hypoplasia of bile duct	Newborn (premature infant 27 weeks)	90 mg/kg/intravenous	Sepsis	Death due to cardiac failure
1992900858-1	Heart murmur, anemia, bronchiolitis, neutropenia, respiratory syncytial virus & rotavirus	1 month	50 mg/kg/oral	Fever/Nasal Staph infection and rhinopharyngeal infection	Recovered
1996004980-1	Therapeutic failure	1 month	6.6 gm/intravenous	Pneumonia	Unknown
1999005047-1	Edema, extravasation	1 month	300 mg/intravenous	Bronchopneumonia	Recovered
1990901582-1	Thrombocytopenia	3 weeks	Unknown	Neonatal sepsis	Unknown
1995009974-1	Losing hair	4 weeks	1125 mg/oral	Cold	Unknown
1987900206-1	Progression of lymphadenitis	3 weeks	Unknown	Enlarged lymph node	Recovered
1999030288-1	Losing weight	11 days	Via breast- milk	N/A	N/A
1998030214-1	Overdose (inadvertent/asymptomatic)	21 days	468.75 mg/oral	Unknown	N/A
1995001302-1	Herpes simplex infection, toxic hepatitis	20 days	1500 mg/oral	Urinary tract infection	Death from Neonatal infection
1994009705-1	Dyspnea, premature birth	1 day	1875 mg/ Exposure	N/A	Recovered
1993900292-1	Severe diarrhea	2 weeks	500 mg/ Via breast-milk	N/A	Unknown
1989901360-1	Jaundice	1 day	1875mg/ Exposure in utero	N/A	Unknown

Information from the Published Literature

A clinical study by Kenyon, et al. (July 1, 1994 until May 31, 2000) titled: Broad-spectrum antibiotics for preterm, prelabor rupture of fetal membranes: the ORACLE I randomized trial. This study described treatment with erythromycin and Augmentin in patients with premature rupture of fetal membranes. In this study, a total of 4826 women with premature rupture of fetal membranes were randomly assigned treatment with either erythromycin 250 mg (n=1197) or Augmentin 250/125 mg (n=1212) or placebo (n=1225) four times daily for ten days or until delivery. The findings of this study were as follows: Among all 2415 infants born to women administered with erythromycin only or placebo, fewer had the primary composite in the erythromycin group (151 of 1190 (12.7%) versus 186 of 1225 (15.2%) than in the placebo group. Among the 2260 singletons in this comparison, significantly fewer had the composite primary outcome in the erythromycin group (125 of 1111 [11.2%] versus 166 of 1149 [14.4%]. Amoxicillin/clavulanate only and amoxicillin/clavulanate plus erythromycin had no benefit over placebo with regard to this outcome in all infants or in singletons only. Use of erythromycin was associated with prolongation of pregnancy, reductions in neonatal treatment with

surfactant, decreases in one of the major findings of the study was that Augmentin only, or Augmentin plus erythromycin, was associated with a significantly higher rate of neonatal NEC. The authors suggested a significantly higher rate of suspected or proven NEC in the Augmentin treatment group compared with the no Augmentin treatment group. The rate of suspected or proven NEC in the Augmentin group alone was 3.7% vs 2.3% in the placebo group. The rate of proven NEC in the Augmentin group was 1.6% vs 0.3% in the placebo group. The rate of suspected or proven NEC with any Augmentin treatment was 3.3% versus 2.0% with no Augmentin. The rate of proven NEC was 1.5% with any Augmentin treatment versus 0.5% with no Augmentin treatment.

Another trial by Kenyon, et al., titled: Broad-spectrum antibiotics for spontaneous preterm labor: the ORACLE II randomized trial, was concurrently conducted with ORACLE I. This study enrolled women at less than 37 weeks gestation who were in suspected or definite preterm labor with intact fetal membranes. A total of 6295 women in spontaneous preterm labor with intact membranes and without evidence of clinical infection were randomly assigned 250 mg erythromycin (n=1611), 325 mg co-amoxicillin/clavulanate (n=1550), both (n=1565), or placebo (n=1569) four times daily for 10 days or until delivery, whichever occurred earlier. Of the 6295 women randomized, 40 were lost to follow-up and 14 had protocol violations; 6241 women were therefore included in the analyses. Results with respect to the incidence of necrotizing enterocolitis in the study were as follows: Suspected or proven cases in the erythromycin and co-amoxicillin/clavulanate were 23 (1.5%); Placebo only group, 12 (0.8%); and erythromycin alone, co-amoxicillin/clavulanate alone, or both, 58 (1.2%). In the proven cases with the erythromycin and co-amoxicillin/clavulanate, 11 (0.7%); the placebo group, 4 (0.3%); and 26 cases (0.6%) in the erythromycin alone, co-amoxicillin/clavulanate alone, or both. There was a higher proportion of neonates with suspected or proven NEC for use of any co-amoxicillin/clavulanate, although these differences were not significant. According to this study, none of the trial antibiotics was associated with a lower rate of the composite primary outcome than placebo (erythromycin 90 [5.6%], co-amoxicillin/clavulanate 76 [5.0%], both antibiotics 91 [5.9%], versus placebo 78 [5.0%]. However, antibiotic prescription was associated with a lower occurrence of maternal infection. The authors interpreted the results of this trial that antibiotics should not be routinely prescribed for women in spontaneous preterm labor without evidence of clinical infection.

A prospective trial of Augmentin prophylaxis in pediatric abdominal surgery conducted by Brereton, et al. in 1985 revealed that those patients who received Augmentin, one infant with Down's syndrome and duodenal atresia developed NEC several weeks later and died. In the comparator arm (metronidazole/gentamicin), one patient died from NEC.

B. Supporting Information for the Addition of Acute Generalized Exanthematous Pustulosis (AGEP)

Background Information

Acute generalized exanthematous pustulosis (AGEP) is characterized by acute formation of numerous small sterile pustules on a widespread erythema, accompanied by fever and leukocytosis which follow an acute infection and/or drug ingestion. The disease is reported to be rapidly self-limiting typically lasting 7 to 10 days. Other alternative terminologies, which have been used, include generalized pustular drug rash, and toxic pustuloderma. The very short interval between drug administration and the onset of the pustular skin reaction is a striking feature of AGEP (the mean onset delay has been reported as 2.5 days in one study of 63 patients. Histopathology of the skin biopsy material shows spongiform subcorneal pustules.

According to the applicant, the primary sources of information used in the database search were the Smithkline Beecham (SB) Worldwide Clinical Safety Database and the medical literature. The medical information databases used in this search include SB's internal literature database (SB Line), Medline, Toxline, Embase, Biosis, Scisearch and Derwent Drug Files and general textbooks (Meyler's and Martindale). The applicant followed the diagnostic criteria to determine whether the reports retrieved from the SB safety database accurately reflect the definition of AGEP, including: acute time to onset; associated with fever; pustules on a widespread erythema; associated with hyperleukocytosis; skin biopsy shows subcorneal pustules; and no mucosal involvement. The applicant noted that it is rare that all of the diagnostic criteria will be reported in a case. However, if most of the above criteria are available and a relevant clinical picture is established, a probable diagnosis can be made, i.e., if a biopsy result is absent, but all other criteria are fulfilled, a probable diagnosis can be made.

MO Comment: ***The majority of reported cases of AGEP came from regulatory sources. No cases were reported from the clinical trials and postmarketing surveillance database. The FDA–Division of Drug Risk Evaluation was consulted for reports of AGEP associated with Augmentin use. Initial search by that Division found 14 reports in AERS using the term, AGEP. Preliminary review of the reports revealed that none of the cases are associated with amoxicillin. Three of the 14 reports are associated with Augmentin. Note: The narratives of cases (AGEP) were excerpted from the applicant's submitted information.***

Results

A total of 39 reports of AGEP were retrieved from the applicant's safety database using the search strategy. These reports consisted of the following:

- 8 reports of generalized acute exanthema pustulosis

- 7 reports of pustular rash
- 5 reports of pustulosis exanthematous
- 3 reports of pustulous lesions
- 2 reports of pustular eruptions
- 2 reports of toxic pustuloderma
- 1 report of acute generalized eczematoid pustulosis
- 1 report of systemic generalized pustules
- 1 report of acute disseminated exanthematous pustulosis
- 1 report of non-generalized acute exanthematous pustulosis
- 1 report of pustulosis/psoriasis aggravated
- 1 report of small pustules on the lips
- 1 report of papular-pustular allergy
- 1 report of erythema multiforme
- 1 report of chicken pox
- 1 report of acne rosacea aggravated
- 1 report of toxidermia
- 1 report of pustular dermatitis of the whole body

The following table by applicant summarizes the 39 reports of pustular drug reaction from SB Clinical Safety database:

Table 2: Reports of Pustular Skin Reactions from the SB Clinical Safety Database

Source	Fatal	Serious	Non-serious	Total *
Clinical Trial	0	0	0	0
Post-Marketing	0	0	0	0
Spontaneous	0	7	5	12
Literature	0	1	1	2
Regulatory	1	24	1	25
Total	**1**	**32**	**7**	**39**

* The total number includes serious and non-serious reports.

MO Comment: ***The applicant included the fatal case in the count of serious cases. The narrative of the fatal case is excerpted from the applicant's report. Note: The table above has been slightly modified by the reviewer as to its format. In addition to the above cases, a separate review included a total of 48 reports of AGEP in patients who received Amoxil products.***

Of the 39 reports, the age of 38 patients was specified and ranged from 5 and 85 years. The mean age was 56 years. According to the report, the male to female distribution was approximately 1:1.

The range of delay of onset was within 8 hours of initiating amoxicillin therapy to four days post therapy. Of the 48 reports, 34 patients developed the AE while receiving amoxicillin therapy, with a range of onset of eight hours to nine days (mean=4.2 days, medain=3 days). Five patients experienced the AE post-therapy of amoxicillin, with a range of onset of one to Four days post-therapy (mean= 1.8 days, median= 1 day). In the remaining 9 reports, the delay to onset was unknown or not specified.

There were 19 of the 48 cases lacked sufficient number of the necessary criteria to make a probable diagnosis of AGEP. These cases were considered by the applicant to be poorly documented and were excluded from further review. Eight of the 48 cases had an alternative diagnosis other than AGEP and were not included in the review.

Case with a Fatal Outcome

Of the 39 reports received by SB, there was one report with a fatal outcome where the patient died from an unrelated infection.

Case #1998023143-2: This was a regulatory report referring to a male patient with a medical history of stroke, multiple pulmonary infections and swallowing disorders. The patient was receiving Augmentin for treatment of a bronchial superinfection and was also receiving concomitant lysine acetylsalicylate, valproic acid, alfuzosine, methylprednisolone, acetylcysteine and nadroparine. The patient later experienced diarrhea. Augmentin was discontinued six days after therapy commenced and replaced with Clamoxyl (amoxicillin) for 13 days, hydroxyzine and roxithromycine. Approximately eight days after Augmentin therapy had ceased (day eight of clamoxyl therapy), the patient developed an erythematous/pustular rashes, generalized exanthema and fever. Acute generalized exanthematous pustulosis was suspected. Relevant laboratory tests revealed an increased neutrophil count (21000/mm3) and a skin biopsy showed pustulosis.The patient was later hospitalized and developed bullae. The patient recovered from the pustular and erythematous rashes, generalized exanthema and fever within eight days, and experienced skin exfoliation. Approximately nine days later the patient died from an unspecified infection.

Cases with Diagnoses of AGEP

Twenty-one of the 48 (44%) cases had sufficient information to make a probable or possible diagnosis of AGEP. These diagnoses of AGEP were determined due to a clinical picture indicative of AGEP and the presence of the majority of the vital diagnostic criteria. The cases were divided into two groups; those of a probable diagnosis of AGEP and those of a possible diagnosis of AGEP. Of the 21 cases, 13 had a probable diagnosis of AGEP. These cases had a diagnostic biopsy result and clincal picture indicative of AGEP. Nine of the 21 reports had a possible diagnosis of AGEP, where there was usually no skin biopsy result or sufficient

diagnostic criteria to make a probable diagnosis. However, according to the applicant, they had sufficient diagnostic information to make a possible diagnosis of AGEP.

The delay to onset was provided in 17 out of these 21 cases. The pustular skin reaction always appeared while the patient was receiving amoxicillin therapy. The range of delay to onset was within 2 hours of starting amoxicillin therapy to day nine of amoxicillin therapy (mean=3 days, median= 2 days).

According to the applicant, spontaneous recovery of the rash was reported in 5 of these 21 cases with a duration of 2-21 days (mean=11 days, median=8 days). In six of the reports, the patients recovered with treatment, the range of duration was 3-20 days (mean=11 days, n=4). The patient was reported to have recovered in an additional 4 cases, but it was not stated whether treatment was provided. The outcome was unknown at the time of reporting in the remaining five cases.

One case (#1997017771-1) had difficulty of initial diagnosis according to the report. At the outset, the reporters considered the diagnosis of pustular psoriasis since the biopsy result was consistent with this. However, the report stated that the spontaneous recovery within 21 days, and the absence of a family history of psoriasis led to an eventual diagnosis of AGEP.

Cases with a Positive Rechallenge: These cases were reported in 3 patients as follows:

- # 1990900385: A 42-year old female who previously had been given penicillin V as oral prophylaxis, without any problems. A year later, the patient received oral amoxicillin 3 g taken an hour before dental treatment (as Amoxil 3 g sachet; Bencard). The patient developed irritation and erythema affecting the chin within 12 hours of taking this preparation. Over the following 48-72 hours, the rash became pustular. According to the report, resolution occurred within one week of onset without scarring or pigmentation. Subsequent episodes always affected the same area, and extension to other sites did not occur. Biopsy showed an intracorneal pustule consisting primarily of neutrophils. Culture of material from the pustules was negative for bacteria, viruses and fungi. Report of the challenge testing with Amoxil 3 g revealed the typical rash within 24 hours. The reaction was also subsequently produced with pure amoxicillin 3 g orally and not with any of the other constituents of Amoxil, according to the report.

- #1996010015-1: This is a literature report of a 53-year old male who developed pruritic erythematous pustular eruption affecting the chest and upper back during oral amoxicillin treatment on three occasions. A double-blind controlled challenge was performed with therapeutic doses of amoxicillin 500 mg three times daily and placebo which were both administered for 8 days. Pustules appeared in the same locations, on the 7th day of amoxicillin treatment. The challenge with placebo was negative.

- # 1997021240-1: This is another literature report of a 41-year old female who developed bilateral erythema on her thighs, thoracic limbs and trunk, one day after starting amoxicillin for an unspecified indication. In the next 3 days, the patient also developed

pustules. The patient took medications prior to the event, including butylsucobolamin (Buskopan), cimetidine (Tagamet) and oxethazaine (Strocain). Skin biopsy was performed which revealed subcorneal pustules filled with polymorphonuclear neutrophils and spongiform pustules of Kogoj. According to the report, the patient was hospitalized five days later with a diagnosis of pustular drug eruption. Amoxicillin was discontinued and the patient was treated with prednisolone. The outcome of the event was not stated at the time of report. However, when amoxicillin was subsequently reintroduced, the event did recur. No further information was provided.

Information from the Published Literature

The applicant provided this brief information on their literature search of AGEP. A review of standard medical texts provided no discussion of AGEP. In textbooks of dermatology, there are no citations of AGEP among drug reactions. According to the applicant, the absence of citations in these textbooks has been attributed to cases unrecognized as AGEP, misdiagnosed as another entity and its very rare incidence.

A study by Roujeau et al., in 1991 retrospectively analyzed 63 observations of AGEP, collected from nine French departments of dermatology of an acute pustular dermatosis, recently named AGEP in the French literature. This study implicated antibiotics as the predominant cause of AGEP, penicillins and macrolide antibiotics accounted for 62% of the suspected drugs. In 18 (29%) of the cases, the cause of AGEP was attributed to amoxicillin. The authors commented that the percentage of skin reactions attributed to the penicillins and macrolides appeared much higher than that of the Boston Collaborative Drug Surveillance Program, where 32% (n=358) reports of allergic skin rashes were attributed to pencillins or macrolides. Reports of AGEP following beta-lactam antibiotic therapy with ampicillin, penicillin, propicillin, cloxacillin and Augmentin have been retrieved from a search of the medical literature. Amoxicillin has been reported in association with AGEP in a number of individual case reports retrieved from the literature. These literature reports were entered in to the applicant's worldwide clinical safety database as discussed in the narratives.

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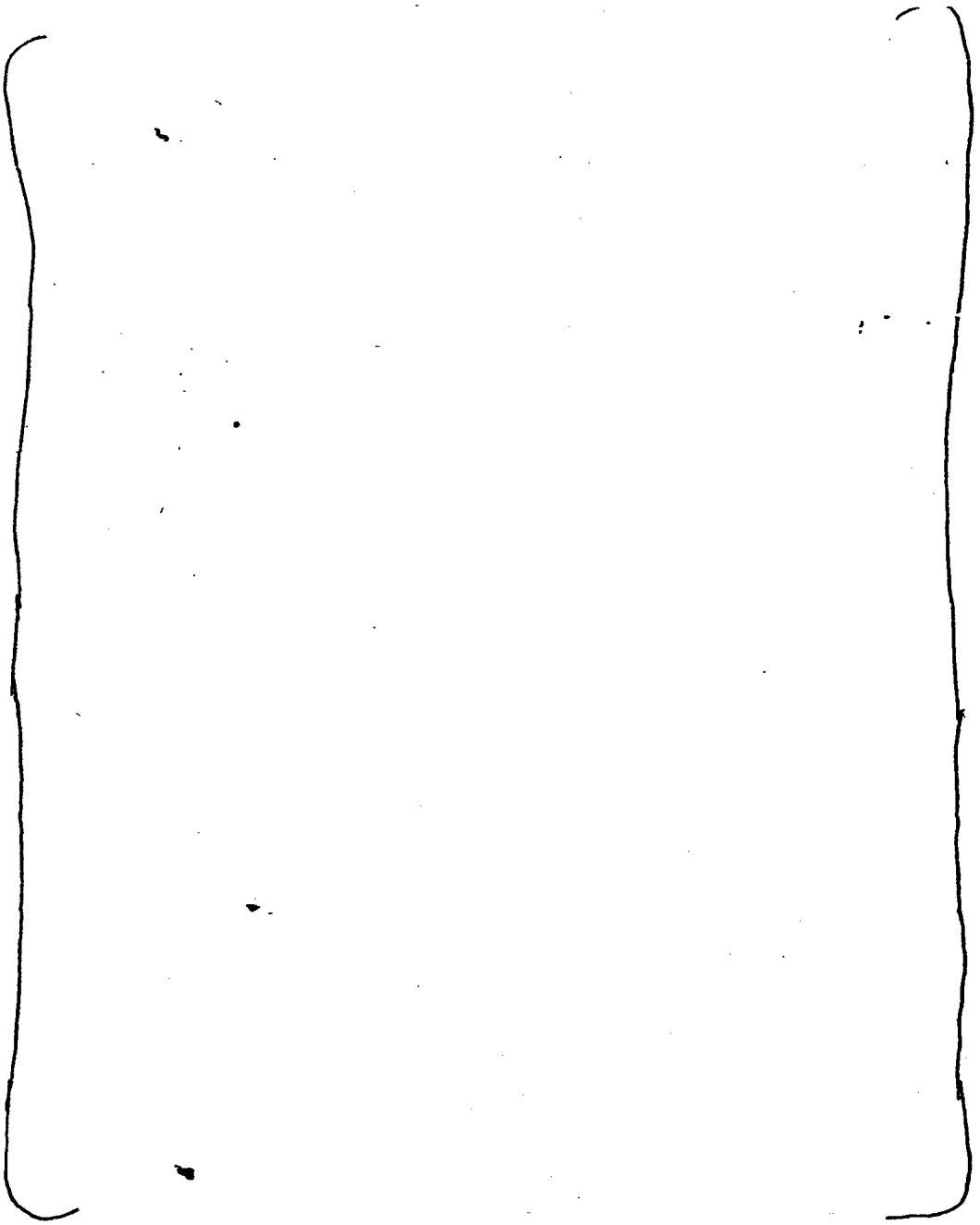
Medical Review A



D. Supporting Information for the Overdosage Section

According to the applicant, a search of the worldwide Clinical Safety database revealed that 148 cases of overdose in patients receiving Augmentin had been received by 14 January

2001. The applicant's definition of an overdose was defined as an adult patient that had taken greater than 12 g of Augmentin per day, or a child under 12 years that had received a daily dose greater than 200 mg/kg. Of the 148 cases 85 patients reported associated symptoms. There was no particular cluster of symptoms reported according to the applicant.

MO Comment: Of the 85 (57%) cases reporting an overdose with associated symptoms, the majority of gastrointestinal symptoms reported include diarrhea (30 cases; 3 loose stools), vomiting/emesis (17 cases), and abdominal pain (10 cases). There were two cases of deaths reported in the applicant's clinical safety database under overdose reports. One case (#1992900226-1), a patient from the UK, age and sex were unknown, committed suicide by taking an intentional overdose of barbiturates while receiving oral Augmentin during a clinical study. Death was reported as due to unknown causes. Medical history includes depression and knee operation. According to the report, the causality was unrelated to the study medication. The second case (#1996003746-1), a 52-year old male, reported by a health professional from ———— USA. This patient received Augmentin 500 mg tid as a 7-day course for pneumonia. On the third day of Augmentin therapy, the patient developed jaundice. However, Augmentin was continued for another three days. According to the report, 7 days later, the patient presented to the emergency room with history of increasing shortness of breath, fatigue and abdominal pain. The patient was then hospitalized for sepsis. According to the report, Augmentin was continued at that time and received a 10-day course. The medical history of this patient includes follicular lymphoma, von Willebrand's disease, Hodgkin's disease, splenectomy, and pneumonia. The patient's condition deteriorated in the hospital with rapid development of overwhelming lactic acidosis over the course of several hours from admission time. Despite resuscitative measures, the patient expired. The principal diagnoses include sepsis, bacterial peritonitis/pleuritis, respiratory failure, acute hepatic failure (cause unknown), acute renal failure probably due to sepsis, coagulopathy, lymphoma, and von Willebrand's disease. The course of the patient's jaundice and therapy with Augmentin were considered by the reporter as to be coincidental. The patient's oncologist reported that the patient's "subacute hepatic necrosis" might be secondary to his lymphoma and chemotherapy rather than the Augmentin therapy. Because of the time course of the patient's condition, drug toxicity was still a possible differential consideration.

5.0 Applicant's Proposed Label for Augmentin contains the following proposed statements for the PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE sections: (Note: The new proposed changes are indicated in bold letters below.)

In the **PRECAUTIONS** section:

> *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.**

In the **ADVERSE REACTIONS** section:

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 exanthematous 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.)

In the **OVERDOSAGE** section:

The applicant proposes that the phrase, "Most patients have been asymptomatic" be deleted in the current Augmentin label. The statement should start with the words, "Following overdosage", which reads as follows:

~~Most patients have been asymptomatic~~ 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.

The revised statement will read as follows:

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.

6.0 Medical Officer's Proposed Label for Augmentin

The applicant's proposed change for the **PRECAUTIONS** section is acceptable.

The applicant's proposed change for the **ADVERSE REACTIONS** section under the *Hypersensitivity Reactions* subsection is acceptable.

[ ]

The applicant's proposed change for the **OVERDOSAGE** section is acceptable.

7.0 Conclusion and Recommendation

It is recommended that the Labeling Supplements for NDA 50-575/S-032, 50-597/S-039, 50-725/S-017, 50-726/S-014, 50-720/S-015, 50-564/S-043, and 50-755/S-003 be approved with the above recommended changes added.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Alma Davidson
4/16/03 03:00:48 PM
MEDICAL OFFICER

John Alexander
4/16/03 03:26:10 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL