CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-755 / S-003

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.

[redacted] THIS WAY
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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] in the OVERDOSAGE section; [redacted] 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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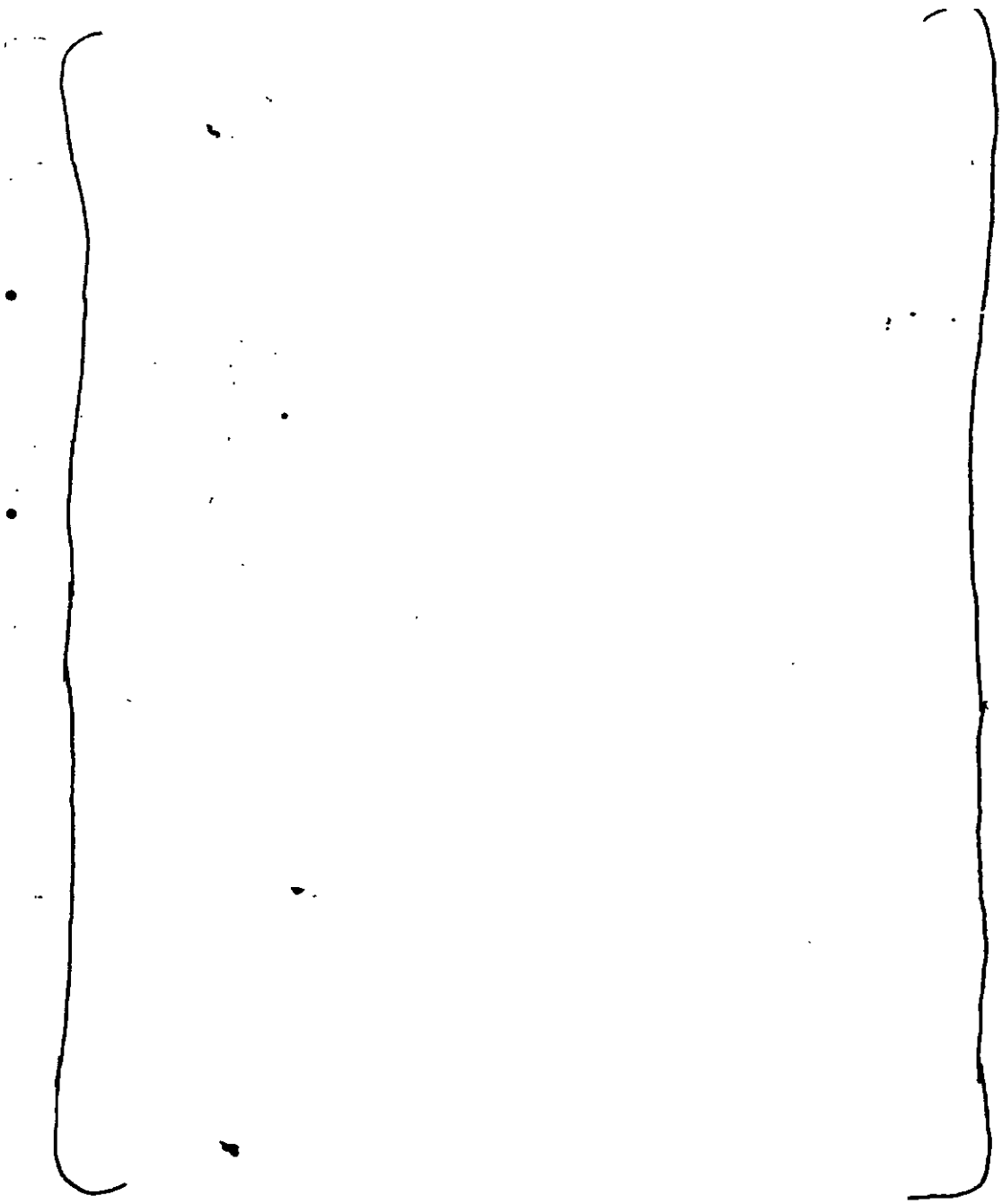
Medical Review A



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.

[redacted]

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
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Medical Review A