CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-785

MEDICAL REVIEW(S)

Medical Officer's Review of Safety Data
Resubmission of NDA 50-785 – Augmentin XR™

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Applicant: GlaxoSmithKline
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P.O. Box 7929
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Drug: Augmentin XR™ (amoxicillin/clavulanate potassium)

Dosage: 1000 mg/62.5 mg Extended Release Tablets

Background:

The New Drug Application for Augmentin XR (amoxicillin/clavulanate potassium) Extended Release Tablets (NDA 50-785) was originally submitted on December 20, 2000 and reviewed by Dr. Charles Cooper. On December 12, 2001, an action was taken on this application, and a "not approvable" letter sent to the applicant. This resubmission is a complete response to the Action Letter.

Dr. Charles Cooper will review the efficacy portion of the resubmission. The integrated summary of safety will be reviewed in this document.

Summary of Safety Data – Original Submission

Please refer to the safety review by Dr. Charles Cooper dated December 20, 2001. A summary of his review is as follows:

The safety database for Augmentin XR included healthy subjects who participated in Clinical Pharmacology studies and patients treated for [redacted] community acquired pneumonia (CAP), and acute bacterial sinusitis (ABS) in Phase 3 clinical studies.

The Integrated Summary of Safety (ISS) included data from 59 patients who participated in three completed Clinical Pharmacology studies (Study 553, Study 558 and Study 583) and 3649 patients (2423 receiving Augmentin XR, 1226 receiving comparator drug) from five active-comparator, controlled clinical studies, one uncontrolled study (Study 551) and an interim analysis of data up to 19 June 2000 from an ongoing, uncontrolled study (Study 547). In addition, the ISS contained a summary of deaths and serious, non-fatal adverse experiences as of the clinical data cut-off of 31 August 2000 from one ongoing, active-comparator, controlled study (Study 557) of patients with CAP. Deaths and

serious, non-fatal adverse experiences which occurred after 19 June 2000 and before the clinical data cut-off of 31 August 2000 in the ongoing portion of CAP Study 547 were also reported.

The mean exposure to Augmentin XR was 8.1 days (N=1199) in controlled studies and 9.4 days (N=1224) in uncontrolled studies. Among the patients who received Augmentin XR in the controlled and uncontrolled studies, 25.2% were treated for —, 33.0% for CAP and 41.9% for ABS. Exposure to Augmentin XR varied by indication. Mean exposure was 7.2 days in the — studies, 8.3 days in the controlled CAP studies (7.4 days in uncontrolled CAP Study 547) and 10.3 days in controlled ABS Study 550 (10.4 days in uncontrolled ABS Study 551).

Overall and within each indication, demographic characteristics were similar between Augmentin XR and all comparator treatment groups. Males and females were represented equally in the Augmentin XR Phase 3 program. The mean age of all Augmentin XR-treated patients was 49 years; 20.8% were ≥65 years old and 8.1% were ≥75 years old. The majority of patients were white and approximately half were enrolled in centers located in the US.

Based on the data provided, the safety profile of Augmentin XR was summarized as follows:

- Augmentin XR demonstrated acceptable safety profile in the three completed Clinical Pharmacology studies and in the controlled and uncontrolled Phase 3 clinical studies. The AE profile of Augmentin XR in combined controlled clinical studies was similar to that in the uncontrolled studies.

- The AE profile of Augmentin XR was similar to that of Augmentin 875/125mg bid in a direct comparison of the two treatments, including gastrointestinal AEs, the body system with the most frequently reported AEs in either treatment group. There was a higher incidence of diarrhea in the study drug (18.0%) vs Augmentin 875 (14.3%) but this failed to reach statistical significance. However, there were twice as many patients with diarrhea in Augmentin XR arm (10 or 3.9%) who required corrective therapy as compared to the Augmentin 875 arm (5 or 1.9%).

- Diarrhea (18.7%) was the only AE reported by ≥5% of Augmentin XR-treated patients overall in the Phase 3 clinical studies. Diarrhea was also the most frequently reported AE for patients who received comparators in the controlled studies (9.2%).

- The AE profile of Augmentin XR was similar to that of levofloxacin-treated patients in combined levofloxacin comparator clinical studies with the exception of diarrhea and genital moniliasis, which were more prevalent in the Augmentin XR group.

- The AE profile of Augmentin XR was similar to that of clarithromycin-treated patients in the clarithromycin comparator clinical study with the exception of diarrhea and genital moniliasis, which were more prevalent in the Augmentin XR group, and taste perversion, which was more prevalent in the clarithromycin group.

- Patient deaths occurred infrequently during the Augmentin XR Phase 3 studies and, for those within 30 days of the cessation of therapy, only in the CAP program. There were more deaths in the Augmentin XR arm; however, upon review, these deaths were not attributable to treatment with Augmentin XR.

- All SAEs associated with death were considered by the investigator to be either unrelated or unlikely to be related to Augmentin XR or comparators.

- No serious AEs occurred during the Clinical Pharmacology studies. In the Phase 3 clinical program, similarly low proportions of patients in the Augmentin XR and All Comparators groups experienced serious AEs on-therapy and within 30 days post-therapy, and few serious AEs were of suspected or probable relationship to study medication. The most frequently reported serious AE was pneumonia in both treatment groups. Two serious AEs of diarrhea were reported as being related to Augmentin XR.

- The serious AE profile of Augmentin XR was comparable to that of patients treated with Augmentin 875/125mg, levofloxacin, and clarithromycin comparators.

- Overall, few subjects who received Augmentin XR in the Clinical Pharmacology studies experienced AEs leading to withdrawal. Non-serious and serious AEs leading to withdrawal occurred infrequently in the controlled and uncontrolled Phase 3 clinical studies. The most frequently reported AE, diarrhea, led to few withdrawals (0.9%) although this was more frequent than withdrawals due to diarrhea in active controls (0.4%).

- The incidence of patients who received Augmentin XR and experienced non-serious and serious AEs leading to withdrawal was generally comparable to that of patients treated with Augmentin 875/125mg b.i.d. or patients treated with either levofloxacin or clarithromycin.

- No pregnancies occurred during the Clinical Pharmacology studies and only two occurred in the Phase 3 clinical program. Each woman delivered a healthy baby girl.

- No remarkable or consistent changes in hematology, clinical chemistry (including liver function) or urinalysis parameters were identified in healthy subjects or in patients who received Augmentin XR in controlled or uncontrolled Phase 3 clinical studies. In addition, laboratory profiles for Augmentin XR-treated patients did not differ markedly from profiles for patients who received Augmentin 875/125mg b.i.d., levofloxacin, or clarithromycin.

- No crystals other than those routinely found in the urine were observed at the on-therapy visit in patients treated with Augmentin XR.

- The tolerability profile of Augmentin XR was not altered when administered concomitantly with Maalox® Antacid (simultaneously and two hours apart). No evidence of a drug-drug interaction was noted.

- Augmentin XR had an acceptable safety profile in patients taking concomitant medications commonly used in [redacted], CAP and ABS. The AE profile of the concomitant drug and/or drug class subgroups, where diarrhea, nausea and headache were the most frequent AEs, was consistent with the AE profile of Augmentin XR in the combined controlled clinical studies, although the rate of diarrhea varied. Specifically, there was a significant increase in the rate of diarrhea in the Augmentin XR arm in those patients taking concomitant drugs which have the ability to increase gastric pH (28.6%) as well as those patients who were taking pseudoephedrine (28.0%) as compared to the overall rate of diarrhea for Augmentin XR patients in all controlled clinical trials (18.7%).

- In Clinical Pharmacology studies, headaches were the most frequently reported AEs and occurred more frequently in females than males. Only female subjects reported genital moniliasis, which occurred in 9.7% of the total subject sessions.

- There were no appreciable differences in the AE profiles reported by gender, age, racial origin or country in the Phase 3 clinical studies. However, the overall proportion of patients reporting AEs was higher in the US compared with the combined non-US centers.

- As with the overall population of patients who received Augmentin XR in the Phase 3 studies, diarrhea and nausea were the most frequently reported AEs within each demographic subgroup examined.

- The AE and laboratory profiles (hematology, clinical chemistry and urinalysis) of Augmentin XR-treated patients were generally similar for patients with [redacted] CAP and ABS. Augmentin XR was generally well tolerated by patients within each indication.

- The AE and laboratory profiles of Augmentin XR-treated patients in combined controlled [redacted] and CAP studies and in the individual controlled ABS study were similar to the AE and laboratory profiles for Augmentin XR-treated patients in the combined controlled studies.

- The profile of serious adverse experiences, including those leading to withdrawal and those associated with death, for the ongoing CAP studies was similar to the profile of the concluded CAP studies (Study 546, Study 556 and an interim analysis of Study 547) with respect to type of serious AE reported and relationship to treatment. Thereby this raised no unique areas of clinical concern.

- There was an increased rate of diarrhea as well as diarrhea and genital moniliasis requiring corrective therapy in the Augmentin XR arm as compared to the other comparators. However, this increased rate did not result in increased serious adverse events or withdrawals secondary to adverse events. The majority of the corrective therapy involved treatment with antidiarrheal medication and very few patients treated with Augmentin XR required more aggressive corrective therapy.

In conclusion, Augmentin XR was safe and generally maintained the safety profile of conventional Augmentin in healthy subjects and in patients treated for [redacted], community acquired pneumonia and acute bacterial sinusitis. There were slightly higher rates of diarrhea and genital moniliasis in the Augmentin XR arm and higher percentages of these patients required corrective therapy, but there were no increases in the rates of serious adverse events or in the drop out rate. In addition, there were higher rates of diarrhea in those patients who were concomitantly taking pseudoephedrine and medications with the potential to raise gastric pH.

Review of Safety Data (Current Application)

Overview

This updated Integrated Summary of Safety (ISS) for Augmentin XR consists of data from six completed, active-comparator controlled clinical studies in — (Study 548 and Study 549), CAP (Study 546, Study 556 and Study 557), and ABS (Study 550). One completed, uncontrolled, open-label, non-comparator study in ABS (Study 551) and interim analyses from two ongoing uncontrolled, open-label, non-comparator studies in CAP (Study 547) and ABS (Study 592) are also included (see Figure 1). This updated ISS describes the safety profile of Augmentin XR based on a total of 4,144 patients receiving the drug product.

This ISS consists of safety data from the controlled studies and the uncontrolled studies for the original NDA (hereafter referred to as NDA) and new studies, combined. The dataset for the new studies contains data from Studies 557 and 592 and from patients in Study 547 who were not included in the first interim report submitted in the original NDA. Any changes to data for patients originally included in the Study 547 1st Interim Report are not reflected in the new studies dataset, but are presented in the combined (NDA and new studies) dataset.

Figure 1: Summary of Phase 3 Clinical Program to Evaluate the Safety of Augmentin XR

All Exposed Patients:	Augmentin XR: N=4144	All Comparators:	n=1387
Controlled Studies:	Augmentin XR: N=1357	All Comparators,	n=1387
Controlled — Studies:	Augmentin XR: N=597	All Comparators:	n=610
Controlled CAP Studies:	Augmentin XR: N=582	All Comparators:	n=595
Controlled ABS Study	Augmentin XR: N=178	All Comparators:	n=182
Uncontrolled Studies:	Augmentin XR: N=2787	(Studies 547, 551, 592)	
Uncontrolled CAP Study	Augmentin XR: N=1122	(Study 547)	
Uncontrolled ABS Studies	Augmentin XR: N=1665	(Studies 551 and 592)	

Figure 1: (cont) Augmentin XR Phase 3 Clinical Program

	CAP	ABS
548 Aug XR: 7 days Clarithromycin 500 mg b.i.d: 7 days	546 Aug XR: 7 days Aug 875/125 mg b.i.d: 7 days	550 Aug XR: 10 days Levofloxacin 500 mg o.d: 10 days
549 Aug XR: 7 days Levofloxacin 500 mg o.d: 7 days	556 Aug XR: 10 days Aug 1000/125mg t.i.d: 10 days	551 (Open) Aug XR: 10 days
	557 Aug XR: 7 or 10 days Aug 875/125 mg t.i.d: 7 or 10 days	592 (Open)** Aug XR: 10 days
	547 (Open)* Aug XR: 7 days	

* Study 547 includes safety data from an interim analysis of patients who completed the study on or before 05 July 2001 and whose data were received by SmithKline Beecham (SB). Patients who reported an SAE or whose SAE data were received after 05 July 2001 but prior to the clinical cut-off date of 31 December 2001 are included in Ongoing Studies.
**Study 592 includes safety data from an interim analysis of patients who completed the study on or before 02 August 2001 and whose data were received by SmithKline Beecham (SB). Patients who reported an SAE or whose SAE data were received after 02 August 2001 but prior to the clinical cut-off date of 31 December 2001 are included in Ongoing Studies.

Medical Officer's Comments:

This review will summarize the overall safety data from the original NDA and the new studies, combined. If there is any difference found in the reports of Adverse Reactions or premature discontinuations or deaths, then those will be discussed in detail.

Extent of Exposure

Methodology

The safety population consisted of all patients who received at least one dose of study medication. Extent of exposure for each patient in the Phase 3 studies was calculated as follows:

Duration of treatment = (stop date - start date) + 1.

Therefore, in a case where study medication started and stopped on the same day, study medication was considered to have been stopped on the first day of dosing and the duration of treatment was 1 day, although the medication was started and stopped on Day 0 relative to the date of first dose.

Where it was not possible to calculate the above, exposure was tabulated as unknown.

Patients frequently initiated therapy with the evening dose and thus took only one dose of study medication on Day 0. Therefore, exposures of 8 days in 7-day treatment studies and 11 days in 10-day treatment studies were common because the patient finished on the morning of the 8th or 11th day of dosing.

Clinical Studies

A total of 4144 patients received Augmentin XR (2000/125mg bid) in six completed double-blind, active-comparator clinical studies (N=1357) and three uncontrolled, non-comparative clinical studies (N=2787).

Controlled Studies

In controlled studies, 1357 patients received Augmentin XR and 1387 received a comparator. The mean duration of exposure was 8.1 days in both the Augmentin XR group and the All Comparators group. The range of exposure was 1 to 22 days in the Augmentin XR group and 1 to 15 days in the All Comparators group.
Augmentin XR was received for 7 or 8 days by 63.1% of patients and for 10 or 11 days by 27.6% of patients. Two patients had a duration of exposure to Augmentin XR of ≥15 days: 548.142.07399 (16 days), and 548.142.07396 (22 days). The investigators confirmed these extended durations and commented that no more than the maximum expected number of tablets were taken. The patients did not initially understand the dosing schedule or were otherwise poorly compliant. In the All Comparators group, one patient (550.414.03545) had an exposure to levofloxacin of 15 days. This extended exposure was also confirmed; the patient had not taken all of the medication by the stop date.

Table 1
Extent of Exposure in Combined Controlled Studies

	Treatment Group			
	Augmentin XR		All Comparators*	
Extent of Exposure (days)	N=1357**		N=1387+	
Mean (SD)	8.1 (2.1)		8.1 (2.0)	
Range	(1.0-22.0)		(1.0-15.0)	
Duration of Therapy (days)	**n**	**(%)**	**n**	**(%)**
1	16	(1.2)	9	(0.6)
2	15	(1.1)	19	(1.4)
3	19	(1.4)	19	(1.4)
4	22	(1.6)	20	(1.4)
5	15	(1.1)	12	(0.9)
6	6	(0.4)	9	(0.6)
7	462	(34.0)	504	(36.3)
8	394	(29.0)	380	(27.4)
9	10	(0.7)	14	(1.0)
10	132	(9.7)	160	(11.5)
11	242	(17.8)	224	(16.1)
>11	11	(0.8)	12	(0.9)
Unknown	13	(1.0)	5	(0.4)

*All Comparators were clarithromycin 500mg bid (N=295), levofloxacin 500mg od (N=497), Augmentin 875/125 mg bid (N= 259) or tid (161) and Augmentin 1000/125mg tid (N=175)
**N=1344 for mean.
+N=1382 for mean.

Uncontrolled Studies

A total of 2787 patients received Augmentin XR in three uncontrolled studies (Study 547: 7 day treatment duration; Studies 551 and 592: 10 day treatment duration). The mean duration of exposure was 9.1 days, with a range of exposure of 1 to 19 days (Table 2 below).

Augmentin XR was received for 7 or 8 days by 35.8% of patients and for 10 or 11 days by 56.3% of patients. Three patients had an exposure to Augmentin XR of ≥15 days: 592.202.19387 (15 days), 547.046.07086 (16 days), and 547.209.08569 (19 days, dosing was interrupted due to hospitalization for worsening pneumonia).

Table 2
Extent of Exposure in Combined Uncontrolled Studies

	Treatment Group Augmentin XR N=2787*	
Extent of Exposure (days)		
Mean (SD)	9.1 (2.0)	
Range	(1-19)	
Duration of Therapy (days)	**N**	**(%)**
1	14	(0.5)
2	23	(0.8)
3	25	(0.9)
4	21	(0.8)
5	22	(0.8)
6	23	(0.8)
7	448	(16.1)
8	550	(19.7)
9	19	(0.7)
10	754	(27.1)
11	816	(29.3)
>11	38	(1.4)
Unknown	34	(1.2)

*N=2753 for mean.

Studies by Indication

The Augmentin XR clinical program consisted of six randomized, double-blind, controlled clinical studies and three uncontrolled studies in — indications. In all studies, Augmentin XR was administered at a dose of 2000/125mg bid.

Extent of exposure is presented by indication in the table below (Table 3) due to variation of the treatment duration by the indication under study.

Table 3
Study Summary by Indication

Indication	Comparator	Treatment Duration
[redacted]		
Study 548	Clarithromycin 500mg bid	7 days
Study 549	Levofloxacin 500mg od	7 days
CAP		
Study 546	Augmentin 875/125mg bid	7 days
Study 556	Augmentin 1000/125mg tid	10 days
Study 547	NA	7 days
Study 557	Augmentin 875/125mg tid	7 or 10 days
ABS		
Study 550	Levofloxacin 500mg od	10 days
Study 551	NA	10 days
Study 592	NA	10 days

In the [redacted] studies the mean duration of exposure was 7.2 days in both the Augmentin XR group and the All Comparators (levofloxacin or clarithromycin) group. The mean duration of exposure in the controlled CAP studies was 8.4 days in the Augmentin XR group and 8.3 days in the All Comparators (Augmentin 875/125mg or Augmentin 1000/125mg) group. In uncontrolled CAP Study 547 (interim analysis up to 19 June 2000), the mean duration was 7.3 days, reflecting the 7-day treatment period. The mean duration of exposure in controlled ABS Study 550 was 10.3 days for Augmentin XR and 10.4 days for levofloxacin. Similarly, mean duration of exposure in uncontrolled ABS Study 551 was 10.4 days.

Medical Officer's Comments:

The mean duration of exposure in this database is similar to what was reported in the original NDA database.

Demography

Clinical Studies

In the Phase 3 program, 4144 patients were treated with Augmentin XR and 1387 patients with comparators. The distribution of patients in the controlled and uncontrolled studies by gender was generally even in the Augmentin XR and All Comparator groups; the majority of patients were white (80.7% in the Augmentin XR group, 92.1% in the All Comparators group). The mean age of patients who received Augmentin XR in the

controlled and uncontrolled studies was 47.3 years, with a range of 16 to 98 years. Among Augmentin XR-treated patients in controlled and uncontrolled studies, 19.2% were ≥65 years old and 7.9% were ≥75 years old. The mean age of patients who received comparator was 48.9 years, with a range of 16 to 98 years; 21.5% were ≥65 years old. The distribution of Augmentin XR-treated patients in the controlled and uncontrolled studies by country was 46.4% from the United States, 42.0% from Europe and 11.6% from other countries.

Table 4: Demography in Controlled Clinical Studies

	Treatment Group	
Demographic Characteristic	**Augmentin XR N=1357**	**All Comparators N=1387**
Age (years) n (%)		
≥16 - <18	2 (0.1)	2 (0.1)
≥18 - <40	241 (17.8)	249 (18.0)
≥40 - <65	666 (49.1)	715 (51.6)
≥65	448 (33.0)	421 (30.4)
Mean (SD)	55.3 (16.6)	54.5 (16.5)
Range	17 – 92	16 – 94
Gender n (%)		
Male	705 (52.0)	722 (52.1)
Female	652 (48.0)	665 (47.9)
Race n (%)		
White	1239 (91.3)	1278 (92.1)
Black	59 (4.3)	57 (4.1)
Oriental	8 (0.6)	7 (0.5)
Other*	51 (3.8)	45 (3.2)
Weight (kg)		
Mean (SD)	77.5 (20.8)	78.4 (20.1)
Median	75	74.8
Range**	20 – 240	28 – 181.4
Region		
United States	622 (45.8)	642 (46.3)
European countries	715 (52.7)	728 (52.5)
Other countries†	20 (1.5)	17 (1.2)

*Includes Arab, Asian, Black Half-Breed, Gypsy, Guyana-Indian, Half-Caste, Hispanic, Indian (Asian), Indonesian, Italian-American, Middle-Eastern, Mixed, Native American, Native-American and German, North African, Pakistani, Polynesian, Portuguese, Spanish, Undisclosed and White-Latin (ISS SAS Datasets)

**For Study 550, a weight of 20 kg was recorded incorrectly in the database and upon checking was found to be 70 kg. The minimum weight in the Augmentin XR group of Study 550 was 41.7 kg.

† Includes Costa Rica, Mexico, Panama and South Africa

Table 5: Demography in Uncontrolled Clinical Studies

Demographic Characteristic	Treatment Group Augmentin XR N=2787
Age (years) n (%)	
≥16 - <18	28 (1.0)
≥18 - <40	1273 (45.7)
≥40- <65	1138 (40.8)
≥65	348 (12.5)
Mean (SD)	43.3 (16.5)
Range	16 – 98
Gender n (%)	
Male	1325 (47.5)
Female	1462 (52.5)
Race n (%)	
White	2105 (75.5)
Black	205 (7.4)
Oriental	216 (7.8)
Other*	261 (9.4)
Weight (kg)	
Mean (SD)	76.6 (19.3)
Median	72
Range	26 – 181.8
Region	
United States	1301 (46.7)
European countries	1025 (36.8)
Other countries**	461 (16.5)

*Includes Arab, Asian, Black Half-Breed, Gypsy, Guyana-Indian, Half-Caste, Hispanic, Indian (Asian), Indonesian, Middle-Eastern, Mixed, Native American, Native-American and German, North African, Pakistani, Polynesian, Portuguese, Spanish, Undisclosed and White Latin (ISS SAS Datasets)

**Includes South Africa, China, Thailand, Mexico, Malaysia, Costa Rica, Philippines, Indonesia, Pakistan, Saudi Arabia and Turkey

Among patients receiving Augmentin XR in the controlled and uncontrolled studies, 14.4% were treated for —, 41.1% for CAP and 44.5% for ABS. The distribution of patients by gender was nearly equal among patients treated for — and CAP; more females than males were treated for ABS. Approximate mean ages for patients treated were 60 years for —, 51 years for CAP, and 41 years for ABS. The majority of patients were white for each indication.

Medical Officer's Comments:

The demographic characteristics in the overall database are similar to the database submitted in the original NDA.

Adverse Experiences

Summary

In the Augmentin XR Phase 3 clinical program, the proportions of all exposed patients that reported at least one AE during the interval on-therapy and within 30 days post-therapy were similar for those treated with Augmentin XR and All Comparators in the three datasets of patients examined: NDA (Augmentin XR: 48.0%, All Comparators: 50.4%), new (Augmentin XR: 46.0%, All Comparators: 57.8%), and combined (NDA and new studies, Augmentin XR: 47.1%, All Comparators: 51.3%). The body system with the greatest proportion of AEs in each dataset examined was the gastrointestinal system for both Augmentin XR and All Comparators. Diarrhea remained the most frequently reported AE in Augmentin XR (combined dataset: 17.4%) and All Comparator-treated patients (combined dataset: 9.9%), requiring corrective treatment in only 4.0% and 2.4% of Augmentin XR and All Comparator-treated patients, respectively, during the on-therapy to 30 days post-therapy interval. At least one AE was considered to be of suspected or probable relation to study medication in 26.2% of patients who received Augmentin XR and 23.3% for All Comparator-treated patients (combined dataset). Most AEs were mild or moderate in severity. The most frequently reported severe AEs for Augmentin XR-treated patients were diarrhea (1.1%), headache (0.4%) and nausea (0.3%), which occurred with similar frequency in All Comparator-treated patients (diarrhea: 0.7%, headache: 0.1% and nausea: 0.6%). In general, first onset of diarrhea occurred Day 1 through Day 3 for all exposed patients in both treatment groups. For Augmentin XR-treated patients reporting diarrhea, frequency of first occurrence was greatest during Day 2 (6.5%). Overall, the AE profiles were similar in all exposed patients treated with Augmentin XR and All Comparators across the three datasets examined (NDA, new and combined).

In the combined controlled studies, the proportion of patients that reported at least one AE during the interval on-therapy and within 30 days post-therapy was also similar between the Augmentin XR group and All Comparators (combined dataset: 52.3% and 51.3%, respectively). The body system with the greatest proportion of AEs in all three datasets was the gastrointestinal system, with a range of 27.2% to 29.1% of patients who received Augmentin XR and 22.7% to 27.3% of patients in the All Comparators group. Diarrhea was the most frequently reported AE during the interval on-therapy to 30 days post therapy in the Augmentin XR group (combined dataset: 19.8%) and All Comparators groups (combined dataset: 9.9%); $P<0.01$ [95% CI: 7.24, 12.47]. Diarrhea required corrective treatment in 4.9% of Augmentin XR patients and 2.4% of All Comparators patients in the combined dataset. At least one AE was considered to be of

suspected or probable relation to study medication in 28.3% (combined dataset) of patients who received Augmentin XR in controlled studies. In All Comparator-treated patients 23.3% reported AEs of suspected or probable relation to study medication in the combined dataset. Diarrhea was the most frequently reported AE of suspected or probable relation to study medication in Augmentin XR-treated patients (combined dataset: 17.8%). The incidence of diarrhea of suspected or probable relation to study medication in All Comparators was 8.7% in the combined dataset. Most AEs were mild or moderate in severity; with similar proportions of severe AEs in the Augmentin XR and All Comparators groups within the NDA, new and combined datasets.

In combined uncontrolled studies, there were 44.9%, 44.3% and 44.6% of Augmentin XR-treated patients in the NDA, new and combined datasets who reported at least one AE during the interval on-therapy and within 30 days post-therapy. The body system with the greatest proportion of patients with at least one AE was the gastrointestinal system (NDA: 26.1%, new: 23.1%, combined: 24.4%). Diarrhea was the most frequently reported AE, occurring in 17.6%, 15.4% and 16.2% of the NDA, new and combined patients in uncontrolled studies receiving Augmentin XR. At least one AE was considered to be of suspected or probable relationship to Augmentin XR in 26.9%, 23.9% and 25.2% of patients in the uncontrolled studies in the NDA, new and combined datasets. The most frequent AE of suspected or probable relationship to study medication was diarrhea (NDA: 16.3%, new: 13.6%; combined: 14.6%). The proportions of patients with severe AEs reported for the Augmentin XR uncontrolled studies was almost identical in the three datasets examined herein (NDA: 5.6%; new: 5.4%; combined dataset: 5.5%). In the combined (NDA and new) dataset, the most frequently reported severe AEs in the uncontrolled studies were diarrhea (1.0%), headache (0.4%) and pneumonia (0.4%).

The AE profile of Augmentin XR 2000/125mg bid was similar to that of Augmentin 875/125mg bid in a direct comparison of the two treatments in CAP Study 546, including gastrointestinal AEs, the body system with the most frequently reported AEs in either treatment group. The most frequently reported AE was diarrhea, which occurred in 18.0% of patients in the Augmentin XR group and in 14.3% of patients in the Augmentin 875/125mg group, however, the difference between the treatment groups was not statistically significant (P=0.28; 95% CI= -2.6%,10.1%). Furthermore, the profile for Augmentin XR did not differ markedly from the established AE profile for Augmentin 875/125mg bid, an approved regimen in the US for the treatment of respiratory tract infections.

Clinical Studies

The clinical study data are summarized in this section by all exposed patients, followed by the controlled clinical studies (Study 546, Study 548, Study 549, Study 550, Study 556 and Study 557) and the uncontrolled clinical studies (Study 547, Study 551, Study 592) for the NDA, new study and combined (NDA and new studies) datasets, respectively. An additional analysis includes a comparison to Augmentin 875/125mg b.i.d. (Study 546)

and to the overall safety profile of conventional Augmentin. In all Phase 3 clinical studies, Augmentin XR was administered at a dose of 2000/125mg b.i.d.

All Exposed Patients

Most Frequent Adverse Experiences by Body System

The proportions of all exposed patients that reported at least one AE during the interval on-therapy and within 30 days post-therapy were similar for those treated with Augmentin XR and All Comparators for the NDA (Augmentin XR: 48.0%, All Comparators: 50.4%), new (Augmentin XR: 46.0%, All Comparators: 57.8%), and combined (NDA and new) datasets (Augmentin XR: 47.1%, All Comparators: 51.3%). The number (%) of patients with the most frequently (≥5% in either treatment group) reported AEs by body system are summarized in the table below. (Table 6)

In all exposed patients, the body system with the greatest proportion of AEs in the NDA, new and combined datasets was the gastrointestinal system. A range of 23.5% to 27.6% of patients who received Augmentin XR and 22.7% to 27.3% of patients in the All Comparators group reported at least one AE in the gastrointestinal system.

Table 6

Number (%) of All Exposed Patients Reporting Adverse Experiences (≥5% in Either Treatment Group) by Body System: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Exposed Patients Treatment Group				New Data All Exposed Patients Treatment Group				Combined NDA +New Data All Exposed Patients Treatment Group			
	Augmentin XR N=2423		All Comparators N=1226		Augmentin XR N=1721		All Comparators N=161		Augmentin XR@ N=4144		All Comparators* N=1387	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	1162	(48.0)	618	(50.4)	791	(46.0)	93	(57.8)	1952	(47.1)	711	(51.3)
Gastrointestinal	669	(27.6)	278	(22.7)	404	(23.5)	44	(27.3)	1073	(25.9)	322	(23.2)
Respiratory	180	(7.4)	131	(10.7)	167	(9.7)	36	(22.4)	345	(8.3)	167	(12.0)
Resistance Mechanism	172	(7.1)	70	(5.7)	103	(6.0)	16	(9.9)	275	(6.6)	86	(6.2)
Body as a Whole	149	(6.1)	87	(7.1)	73	(4.2)	9	(5.6)	221	(5.3)	96	(6.9)
Central and Peripheral Nervous	144	(5.9)	78	(6.4)	98	(5.7)	8	(5.0)	242	(5.8)	86	(6.2)
Musculoskeletal	64	(2.6)	48	(3.9)	47	(2.7)	9	(5.6)	113	(2.7)	57	(4.1)
Liver and Biliary	35	(1.4)	18	(1.5)	47	(2.7)	11	(6.8)	83	(2.0)	29	(2.1)

* All Comparators are: Augmentin 875/125 mg bid, Augmentin 875/125 mg tid, Augmentin 1000/125 mg tid, Clarithromycin 500mg bid, and Levofloxacin 500mg od.
@ Any changes to data for patients originally included in the study 547 first Interim Report are not reflected in the new studies dataset, but are presented in the combined (NDA and new studies) dataset

Medical Officer's Comments:

There is no difference in the ADRs reported in the original NDA database versus those reported in the combined NDA database.

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Most Frequent Adverse Experiences by Preferred Term

In all Augmentin XR exposed patients, during the interval on therapy and within 30 days post-therapy, only small changes (1-2%) were noted with respect to overall adverse experiences between the NDA, new, and combined (NDA and new) datasets (Table 7). For all exposed patients who received Augmentin XR, the overall incidence of AEs was similar between the original NDA (48.0%), new (46.0%) and combined datasets (47.1%). The overall incidence of AEs was also similar for All Comparator-treated patients: 50.4% in the NDA, 57.8% in the new and 51.3% in the combined dataset.

For all exposed patients, diarrhea remained the most frequently reported AE in the Augmentin XR group (NDA: 18.8%; new data: 15.7%; combined data: 17.4%). The incidence of diarrhea in the All Comparator-treated patients was 9.3%, 14.9% and 9.9% in the NDA, new and combined dataset, respectively.

Diarrhea required corrective treatment in all exposed patients in only 4.0% of Augmentin XR and 2.4% of All Comparator-treated patients in the combined dataset during the on-therapy to 30 days post-therapy interval.

Medical Officer's Comments:

In the original NDA database, patients with diarrhea who required corrective therapy in Augmentin XR arm was 3.9% compared to 1.9% in the Augmentin 875 arm.

Table 7: Summary of the Most Frequently Reported Adverse Experiences (≥1% in Any Treatment Group*) in All Exposed Patients: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Exposed Patients Treatment Group				New Data All Exposed Patients Treatment Group				Combined NDA +New Data All Exposed Patients Treatment Group			
	Augmentin XR N=2423		All Comparators N=1226		Augmentin XR N=1721		All Comparators N=161		Augmentin XR@ N=4144		All Comparators N=1387	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	1162	(48.0)	618	(50.4)	791	(46.0)	93	(57.8)	1952	(47.1)	711	(51.3)
Diarrhea	455	(18.8)	114	(9.3)	270	(15.7)	24	(14.9)	720	(17.4)	138	(9.9)
Nausea	99	(4.1)	69	(5.6)	39	(2.3)	3	(1.9)	138	(3.3)	72	(5.2)
Headache	88	(3.6)	43	(3.5)	68	(4.0)	4	(2.5)	156	(3.8)	47	(3.4)
Abdominal Pain	60	(2.5)	40	(3.3)	43	(2.5)	8	(5.0)	103	(2.5)	48	(3.5)
Moniliasis Genital (Candidiasis)	54	(2.2)	8	(0.7)	35	(2.0)	2	(1.2)	90	(2.2)	10	(0.7)
Injury	46	(1.9)	24	(2.0)	11	(0.6)	0		57	(1.4)	24	(1.7)
Insomnia	41	(1.7)	23	(1.9)	25	(1.5)	4	(2.5)	66	(1.6)	27	(1.9)
Vomiting	40	(1.7)	21	(1.7)	35	(2.0)	7	(4.3)	75	(1.8)	28	(2.0)
Rhinitis	37	(1.5)	29	(2.4)	21	(1.2)	1	(0.6)	58	(1.4)	30	(2.2)
Dyspepsia	31	(1.3)	13	(1.1)	25	(1.5)	4	(2.5)	56	(1.4)	17	(1.2)
Rash	29	(1.2)	12	(1.0)	11	(0.6)	0		41	(1.0)	12	(0.9)
Upper Respiratory Tract Infection	28	(1.2)	7	(0.6)	20	(1.2)	4	(2.5)	48	(1.2)	11	(0.8)
Dizziness	26	(1.1)	15	(1.2)	16	(0.9)	1	(0.6)	42	(1.0)	16	(1.2)
Gastrointestinal Disorder NOS	25	(1.0)	6	(0.5)	28	(1.6)	2	(1.2)	58	(1.4)	8	(0.6)
Infection Fungal	25	(1.0)	10	(0.8)	4	(0.2)	0		29	(0.7)	10	(0.7)
Pharyngitis	24	(1.0)	20	(1.6)	20	(1.2)	1	(0.6)	44	(1.1)	21	(1.5)
Flatulence	23	(0.9)	15	(1.2)	12	(0.7)	0		35	(0.8)	15	(1.1)
Moniliasis	22	(0.9)	13	(1.1)	5	(0.3)	2	(1.2)	26	(0.6)	15	(1.1)
Myalgia	21	(0.9)	13	(1.1)	11	(0.6)	0		34	(0.8)	13	(0.9)
Sinusitis	20	(0.8)	20	(1.6)	11	(0.6)	0		31	(0.7)	20	(1.4)
Constipation	20	(0.8)	13	(1.1)	12	(0.7)	4	(2.5)	32	(0.8)	17	(1.2)
Pneumonia	20	(0.8)	10	(0.8)	35	(2.0)	8	(5.0)	54	(1.3)	18	(1.3)

Table 7 (cont)
Summary of the Most Frequently Reported Adverse Experiences (≥1% in Any Treatment Group*) in All Exposed Patients: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Exposed Patients Treatment Group				New Data All Exposed Patients Treatment Group				Combined NDA +New Data All Exposed Patients Treatment Group			
	Augmentin XR N=2423		All Comparators N=1226		Augmentin XR N=1721		All Comparators N=161		Augmentin XR N=4144		All Comparators N=1387	
Preferred Term	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Arthralgia	17	(0.7)	9	(0.7)	10	(0.6)	4	(2.5)	27	(0.7)	13	(0.9)
Bronchitis	16	(0.7)	14	(1.1)	13	(0.8)	9	(5.6)	29	(0.7)	23	(1.7)
SGPT Increased	15	(0.6)	9	(0.7)	19	(1.1)	2	(1.2)	34	(0.8)	11	(0.8)
Creatine Phosphokinase Increased	15	(0.6)	8	(0.7)	17	(1.0)	0		32	(0.8)	8	(0.6)
Back Pain	14	(0.6)	20	(1.6)	10	(0.6)	3	(1.9)	24	(0.6)	23	(1.7)
Mouth Dry	14	(0.6)	15	(1.2)	9	(0.5)	0		23	(0.6)	15	(1.1)
Dyspnea	13	(0.5)	6	(0.5)	17	(1.0)	0		30	(0.7)	6	(0.4)
Respiratory Disorder	12	(0.5)	7	(0.6)	10	(0.6)	5	(3.1)	22	(0.5)	12	(0.9)
Taste Perversion	11	(0.5)	38	(3.1)	6	(0.3)	0		17	(0.4)	38	(2.7)
Hematuria	11	(0.5)	7	(0.6)	10	(0.6)	5	(3.1)	21	(0.5)	12	(0.9)
Herpes Simplex	10	(0.4)	9	(0.7)	12	(0.7)	6	(3.7)	22	(0.5)	15	(1.1)
Hepatic Enzymes Increased	9	(0.4)	1	(0.1)	9	(0.5)	5	(3.1)	18	(0.4)	6	(0.4)
Hemoptysis	4	(0.2)	2	(0.2)	13	(0.8)	4	(2.5)	17	(0.4)	6	(0.4)
Pleural Effusion	1	(<0.1)	5	(0.4)	8	(0.5)	4	(2.5)	9	(0.2)	9	(0.6)
Phlebitis	0		1	(0.1)	7	(0.4)	4	(2.5)	7	(0.2)	5	(0.4)

Note: All Comparators for combined NDA+new data are: Augmentin 875/125 mg bid, Augmentin 875/125 mg tid, Augmentin 1000/125 mg tid, clarithromycin 500mg bid, and Levofloxacin 500mg od. All Compapators for new data: Augmentin 875/125 mg tid

*Due to the smaller sample size, the AE frequency cut-off for the all exposed comparators is ≥ 2%., unless an AE is displayed based on ≥1% Frequency in another group

@ Any changes to data for patients originally included in the study 547 first Interim Report are not reflected in the new studies dataset, but are presented in the combined (NDA and new studies) dataset

Adverse Experiences by Relationship to Study Medication

The number (%) of all exposed patients with the most frequently reported AEs of suspected or probable relation to study medication, during the on-therapy to 30 days post-therapy interval, by preferred term, are summarized in the table below. (Table 8)

In all exposed patients, during the interval on therapy and within 30 days post-therapy, at least one AE was considered to be of suspected or probable relation to study medication in 27.8% (NDA), 24.0% (new data) and 26.2% (combined data), of patients who received Augmentin XR. Similar overall frequencies were reported for AEs of suspected or probable relation in All Comparator-treated patients: 23.9% in the NDA, 18.6% in the new and 23.3% in the combined dataset.

For all exposed Augmentin XR-treated patients, diarrhea remained the most frequently reported AE of suspected or probable relation to study medication (NDA: 17.1%; new data: 13.9%; combined data: 15.6%). The incidence of diarrhea of suspected or probable relation to study medication in All Comparators was: 8.1%, 13.0% and 8.7% in the NDA, new and combined datasets, respectively.

In all exposed patients, additional AEs of suspected or probable relation to study medication in the Augmentin XR combined dataset were: nausea (2.2%), genital moniliasis (Candidiasis: 2.1%) and abdominal pain (1.6%). In the All Comparators combined dataset, additional AEs of suspected or probable relationship to study medication included: nausea (4.0%), taste perversion (2.5%) and abdominal pain (2.2%).

Table 8

Summary of the Most Frequently Reported Adverse Experiences (≥1% in Any Treatment Group) of Suspected/Probable Relationship to Study Medication in All Exposed Patients: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Exposed Patients Treatment Group				New Data All Exposed Patients Treatment Group				Combined NDA +New Data All Exposed Patients Treatment Group			
	Augmentin XR N=2423		All Comparators N=1226		Augmentin XR N=1721		All Comparators N=161		Augmentin XR N=4144*		All Comparators N=1387	
Preferred Term	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE of suspected/probable relationship to study medication	673	(27.8)	293	(23.9)	413	(24.0)	30	(18.6)	1086	(26.2)	323	(23.3)
Diarrhea	414	(17.1)	99	(8.1)	239	(13.9)	21	(13.0)	648	(15.6)	120	(8.7)
Nausea	66	(2.7)	55	(4.5)	24	(1.4)	1	(0.6)	90	(2.2)	56	(4.0)
Moniliasis Genital (Candidiasis)	52	(2.1)	8	(0.7)	33	(1.9)	2	(1.2)	86	(2.1)	10	(0.7)
Abdominal Pain	40	(1.7)	27	(2.2)	27	(1.6)	3	(1.9)	67	(1.6)	30	(2.2)
Gastrointestinal Disorder NOS	24	(1.0)	3	(0.2)	27	(1.6)	1	(0.6)	56	(1.4)	4	(0.3)
Flatulence	20	(0.8)	12	(1.0)	10	(0.6)	0		30	(0.7)	12	(0.9)
Dyspepsia	18	(0.7)	13	(1.1)	15	(0.9)	2	(1.2)	33	(0.8)	15	(1.1)
Vomiting	16	(0.7)	12	(1.0)	14	(0.8)	2	(1.2)	30	(0.7)	14	(1.0)
Taste Perversion	11	(0.5)	35	(2.9)	6	(0.3)	0		17	(0.4)	35	(2.5)
Hepatic Enzymes Increased	4	(0.2)	1	(0.1)	2	(0.1)	2	(1.2)	6	(0.1)	3	(0.2)

*Any changes to data for patients originally included in the study 547 first Interim Report are not reflected in the new studies dataset, but are presented in the combined (NDA and new studies) dataset

Adverse Experiences by Severity

Most AEs were mild or moderate in severity (Table 9). In all exposed patients, there were ≤6.6% of Augmentin XR-treated patients and ≤9.0% of All Comparators-treated patients who reported a severe AE in the NDA, new or combined datasets.
In all exposed patients, the most frequently reported severe AEs for Augmentin XR-treated patients were diarrhea (1.1%), headache (0.4%) and nausea (0.3%) in the combined dataset. Severe diarrhea and nausea occurred with similar frequency in All Comparators-treated patients in the combined dataset (diarrhea: 0.7%, headache: 0.1%, and nausea: 0.6%).

Table 9: Number (%) of Patients With at Least One Adverse Experience, by Severity in All Exposed Patients: Original NDA, New Data and Combined (On-Therapy and Within 30 days Post-Therapy

	NDA All Exposed Patients Treatment Group				New Data All Exposed Patients Treatment Group				Combined NDA +New Data All Exposed Patients Treatment Group			
	Augmentin XR N=2423		All Comparators N=1226		Augmentin XR N=1721		All Comparators N=161		Augmentin XR@ N=4144		All Comparators N=1387	
Preferred Term	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**
Patients with at least one AE	1162	(48.0)	618	(50.4)	791	(46.0)	93	(57.8)	1952	(47.1)	711	(51.3)
Mild	799	(33.0)	392	(32.0)	561	(32.6)	77	(47.8)	1362	(32.9)	469	(33.8)
Moderate	554	(22.9)	325	(26.5)	364	(21.2)	43	(26.7)	916	(22.1)	368	(26.5)
Severe*	160	(6.6)	110	(9.0)	89	(5.2)	5	(3.1)	249	(6.0)	115	(8.3)

@ Any changes to data for patients originally included in the study 547 first Interim Report are not reflected in the new studies dataset, but are presented in the combined (NDA and new studies) dataset
*Includes unknown severity.

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Controlled Studies

The controlled clinical studies consisted of two——— studies (Study 548, Study 549) with a treatment duration of 7 days, one CAP study (Study 546) with a treatment duration of 7 days, one CAP study (Study 556) with a treatment duration of 10 days, one CAP study (Study 557) with a treatment duration of 7 or 10 days, and one ABS study (Study 550) with a treatment duration of 10 days.

Comparators in the controlled studies included levofloxacin 500mg o.d. (Study 549 and Study 550), clarithromycin 500mg b.i.d. (Study 548), Augmentin 875/125mg b.i.d. (Study 546), Augmentin 1000/125mg t.i.d. (Study 556) and Augmentin 875/125mg t.i.d. (Study 557).

Most Frequent Adverse Experiences by Body System

The proportions of patients that reported at least one AE during the interval on-therapy and within 30 days post-therapy ranged from 50.4% to 62.0% in either treatment group in the three datasets: NDA (Augmentin XR: 51.0%, All Comparators: 50.4%), new (Augmentin XR: 62.0%, All Comparators: 57.8%), and combined dataset (Augmentin XR: 52.3%, All Comparators: 51.3%). CAP Study 557 was the only new controlled study.

The number (%) of patients with the most frequently (≥5% in either treatment group) reported AEs, during the on-therapy to 30 days post-therapy interval, by body system are summarized in the table below. (Table 10)

In the controlled studies, the proportion of patients that reported at least one AE during the interval on-therapy and within 30 days post-therapy was similar between the Augmentin XR group and All Comparators in the combined (NDA and new) dataset (52.3% and 51.3%, respectively).

The body system with the greatest proportion of AEs in the NDA, new and combined dataset was the gastrointestinal system. A range of 27.2% to 29.1% of patients who received Augmentin XR and 22.7% to 27.3% of patients in the All Comparators group reported at least one AE in the gastrointestinal system. In the combined dataset, the proportion of patients that reported gastrointestinal AEs was 28.9% for Augmentin XR-treated patients and 23.2% for All Comparator-treated patients.

Table 10: Number (%) of Patients Reporting Adverse Experiences (≥5% in Either Treatment Group) by Body System in Combined Controlled Studies: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Controlled Studies Treatment Group				New Data Controlled Study 557 Treatment Group				Combined NDA and New Data All Controlled Studies Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226		Augmentin XR N=158		Augmentin 875/125 mg tid N=161		Augmentin XR N=1357		All Comparators* N=1387	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE	612	(51.0)	618	(50.4)	98	(62.0)	93	(57.8)	710	(52.3)	711	(51.3)
Gastrointestinal	349	(29.1)	278	(22.7)	43	(27.2)	44	(27.3)	392	(28.9)	322	(23.2)
Respiratory	114	(9.5)	131	(10.7)	29	(18.4)	36	(22.4)	143	(10.5)	167	(12.0)
Resistance Mechanism	110	(9.2)	70	(5.7)	6	(3.8)	16	(9.9)	116	(8.5)	86	(6.2)
Body as a Whole	82	(6.8)	87	(7.1)	9	(5.7)	9	(5.6)	91	(6.7)	96	(6.9)
Central and Peripheral Nervous	69	(5.8)	78	(6.4)	19	(12.0)	8	(5.0)	88	(6.5)	86	(6.2)
Musculoskeletal System	37	(3.1)	48	(3.9)	8	(5.1)	9	(5.6)	45	(3.3)	57	(4.1)
Liver and Biliary System	18	(1.5)	18	(1.5)	8	(5.1)	11	(6.8)	26	(1.9)	29	(2.1)

*All Comparators are: Augmentin 875/125 mg b.i.d., Augmentin 875/125 mg t.i.d., Augmentin 1000/125 mg t.i.d., Clarithromycin 500mg b.i.d., and Levofloxacin 500mg o.d.

Most Frequent Adverse Experiences by Preferred Term

In the controlled studies, the most frequently reported AE, during the on-therapy to 30 days post-therapy interval in both treatment groups in the combined NDA and new studies dataset was diarrhea, which occurred in a greater proportion of patients in the Augmentin XR group than in the All Comparators group (19.8% and 9.9% respectively; P<0.01 [95% CI: 7.24, 12.47].

Diarrhea was also the most frequently reported AE during the on-therapy to 30 days post-therapy interval in Augmentin XR-treated patients in the NDA (20.0%) and new studies dataset (18.4%). The incidence of diarrhea in All Comparator-treated patients was: 9.3% and 14.9% in the NDA and new studies dataset, respectively.

During the on-therapy to 30 days post-therapy interval in controlled studies, diarrhea required corrective treatment in 4.9% of Augmentin XR patients and 2.4% of All Comparators patients in the combined dataset.

Nausea, the second most frequently reported AE in the combined dataset, occurred with similar frequency for the Augmentin XR and All Comparators groups (4.3% and 5.2%, respectively; P=0.30 [95% CI: -2.44, 0.74].

Table 11: Summary of the Most Frequently Reported Adverse Experiences (≥1% in Any Treatment Group) in Combined Controlled Studies: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Controlled Studies Treatment Group				New Data Controlled Study 557 Treatment Group				Combined NDA +New Data All Controlled Studies Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226		Augmentin XR N=158		Augmentin 875/125 mg tid N=161		Augmentin XR N=1357		All Comparators N=1387	
Preferred Term	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	N	(%)
Patients with at least one AE	612	(51.0)	618	(50.4)	98	(62.0)	93	(57.8)	710	(52.3)	711	(51.3)
Diarrhea	240	(20.0)	114	(9.3)	29	(18.4)	24	(14.9)	269	(19.8)	138	(9.9)
Nausea	58	(4.8)	69	(5.6)	1	(0.6)	3	(1.9)	59	(4.3)	72	(5.2)
Headache	45	(3.8)	43	(3.5)	13	(8.2)	4	(2.5)	58	(4.3)	47	(3.4)
Moniliasis Genital	31	(2.6)	8	(0.7)	0		2	(1.2)	31	(2.3)	10	(0.7)
Abdominal Pain	29	(2.4)	40	(3.3)	8	(5.1)	8	(5.0)	37	(2.7)	48	(3.5)
Rhinitis	24	(2.0)	29	(2.4)	1	(0.6)	1	(0.6)	25	(1.8)	30	(2.2)
Insomnia	22	(1.8)	23	(1.9)	2	(1.3)	4	(2.5)	24	(1.8)	27	(1.9)
Vomiting	21	(1.8)	21	(1.7)	6	(3.8)	7	(4.3)	27	(2.0)	28	(2.0)
Infection Viral	19	(1.6)	10	(0.8)	2	(1.3)	0		21	(1.5)	10	(0.7)
Upper Respiratory Tract Infection	19	(1.6)	7	(0.6)	0		4	(2.5)	19	(1.4)	11	(0.8)
Injury	17	(1.4)	24	(2.0)	0		0		17	(1.3)	24	(1.7)
Sinusitis	15	(1.3)	20	(1.6)	1	(0.6)	0		16	(1.2)	20	(1.4)
Moniliasis	15	(1.3)	20	(1.6)	0		2	(1.2)	15	(1.1)	22	(1.6)
Dyspepsia	15	(1.3)	13	(1.1)	4	(2.5)	4	(2.5)	19	(1.4)	17	(1.2)
Pharyngitis	15	(1.3)	13	(1.1)	3	(1.9)	1	(0.6)	18	(1.3)	14	(1.0)
Infection Fungal	15	(1.3)	10	(0.8)	0		0		15	(1.1)	10	(0.7)

Table 11 (cont.) Summary of the Most Frequently Reported Adverse Experiences (≥1% in Any Treatment Group*) in Combined Controlled Studies: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Controlled Studies Treatment Group				New Data Controlled Study 557 Treatment Group				Combined NDA +New Data All Controlled Studies Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226		Augmentin XR N=158		Augmentin 875/125 mg tid N=161		Augmentin XR N=1357		All Comparators** N=1387	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**
Bronchitis	13	(1.1)	14	(1.1)	4	(2.5)	9	(5.6)	17	(1.3)	23	(1.7)
Constipation	13	(1.1)	13	(1.1)	1	(0.6)	4	(2.5)	14	(1.0)	17	(1.2)
Rash	13	(1.1)	12	(1.0)	0		0		13	(1.0)	12	(0.9)
Chest Pain	13	(1.1)	9	(0.7)	1	(0.6)	0		14	(1.0)	9	(0.6)
Fatigue	12	(1.0)	11	(0.9)	0		0		12	(0.9)	11	(0.8)
Myalgia	11	(0.9)	13	(1.1)	2	(1.3)	0		13	(1.0)	13	(0.9)
Pneumonia	11	(0.9)	10	(0.8)	6	(3.8)	8	(5.0)	17	(1.3)	18	(1.3)
Dizziness	10	(0.8)	15	(1.2)	2	(1.3)	1	(0.6)	12	(0.9)	16	(1.2)
Arthralgia	10	(0.8)	9	(0.7)	3	(1.9)	4	(2.5)	13	(1.0)	13	(0.9)
Back Pain	9	(0.8)	20	(1.6)	1	(0.6)	3	(1.9)	10	(0.7)	23	(1.7)
Mouth Dry	9	(0.8)	15	(1.2)	0		0		9	(0.7)	15	(1.1)
Flatulence	8	(0.7)	15	(1.2)	1	(0.6)	0		9	(0.7)	15	(1.1)
Asthenia	8	(0.7)	6	(0.5)	4	(2.5)	2	(1.2)	12	(0.9)	8	(0.6)
Herpes Simplex	7	(0.6)	9	(0.7)	4	(2.5)	6	(3.7)	11	(0.8)	15	(1.1)

*Due to the smaller sample size, the AE frequency cut-off for Controlled Study 557 is ≥2%, unless an AE is already displayed based on ≥1% frequency in another group
**All Comparators are: Augmentin 875/125 mg bid, Augmentin 875/125 mg tid (new data-only), Augmentin 1000/125 mg tid, clarithromycin 500mg bid, and levofloxacin 500mg od.

Table 11 (cont.) Summary of the Most Frequently Reported Adverse Experiences (≥1% in Any Treatment Group*) in Combined Controlled Studies: Original NDA, New Data and Combined (On-Therapy and Within 30 Days Post-Therapy)

	NDA All Controlled Studies Treatment Group				New Data Controlled Study 557 Treatment Group				Combined NDA +New Data All Controlled Studies Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226		Augmentin XR N=158		Augmentin 875/125 mg tid N=161		Augmentin XR N=1357		All Comparators** N=1387	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**
Respiratory Disorder	7	(0.6)	7	(0.6)	2	(1.3)	5	(3.1)	9	(0.7)	12	(0.9)
Taste Perversion	6	(0.5)	38	(3.1)	0		0		6	(0.4)	38	(2.7)
Hematuria	5	(0.4)	7	(0.6)	1	(0.6)	5	(3.1)	6	(0.4)	12	(0.9)
Hepatic Enzymes Increased	5	(0.4)	1	(0.1)	4	(2.5)	5	(3.1)	9	(0.7)	6	(0.4)
Pleural Effusion	1	(0.1)	5	(0.4)	6	(3.8)	4	(2.5)	7	(0.5)	9	(0.6)
Hemoptysis	0		2	(0.2)	6	(3.8)	4	(2.5)	6	(0.4)	6	(0.4)
Phlebitis	0		1	(0.1)	5	(3.2)	4	(2.5)	5	(0.4)	5	(0.4)

*Due to the smaller sample size, the AE frequency cut-off for Controlled Study 557 is ≥ 2%, unless an AE is already displayed based on ≥1% frequency in another group
**All Comparators are: Augmentin 875/125 mg b.i.d., Augmentin 875/125 mg t.i.d. (new data-only), Augmentin 1000/125 mg t.i.d., clarithromycin 500mg b.i.d., and levofloxacin 500mg o.d.

Medical Officer's Comments:

APPEARS THIS WAY
ON ORIGINAL

In the combined dataset, the frequency of AEs for Augmentin XR-treated patients in the controlled studies (52.3%) was slightly higher than that in all exposed patients (47.1%) for the on-therapy and within 30 days post-therapy interval.

APPEARS THIS WAY
ON ORIGINAL

Comparison With Established Augmentin 875/125mg Adverse Experience Profile

The AE profile of all exposed Augmentin XR-treated patients was compared to the established Augmentin 875/125mg b.i.d. AE profile, which comprises patient data obtained from Study 233 (pyelonephritis, complicated UTIs) and Study 234 (AECB, CAP). These studies were conducted to support NDA 50-720 approximately six years ago, and analyzed AEs in multinational, blinded, comparator trials comparing different formulations of Augmentin (875/125mg b.i.d with 500/125mg t.i.d.) and were conducted within the FDA clinical trial practice guidelines. These pivotal studies are discussed in more detail within NDA 50-720. Notably, the Study 546 Augmentin 875/125mg AE profile was consistent with this established Augmentin 875/125mg AE profile.

During the interval on-therapy and within 30 days post-therapy, similar proportions of patients in the Augmentin XR and Augmentin 875/125mg treatment groups (47.1% and 49.1%, respectively) reported at least one AE (Table 12). The most frequently reported AE was diarrhea which occurred in 17.4% of patients in the Augmentin XR group and 14.9% of patients in the Augmentin 875/125mg group. Headache was reported by 3.8% and 6.8% of patients in the Augmentin XR and Augmentin 875/125mg groups, respectively, while nausea was reported by 3.3% and 7.9% of patients taking Augmentin XR and Augmentin 875/125mg, respectively. These results further support that the AE profile of Augmentin XR is similar to that of the AE profile for Augmentin 875/125mg b.i.d.

Table 12:
Number (%) of Patients With the Most Frequently Occurring (≥1% in Either Treatment Group) Augmentin XR versus Established Profile for Augmentin 875/125mg (On-Therapy and Within 30 Days Post-Therapy)

Preferred Term	Augmentin XR N=4144		Augmentin 875/125mg N=584	
	n	(%)	n	(%)
Patients with at least one AE	1952	(47.1)	287	(49.1)
Diarrhea	720	(17.4)	87	(14.9)
Headache	156	(3.8)	40	(6.8)
Nausea	138	(3.3)	46	(7.9)
Abdominal Pain	103	(2.5)	26	(4.5)
Moniliasis Genital (Candidiasis)	90	(2.2)	21	(3.6)
Vomiting	75	(1.8)	22	(3.8)
Insomnia	66	(1.6)	6	(1.0)
Rhinitis	58	(1.4)	3	(0.5)
Gastrointestinal Disorder NOS	58	(1.4)	1	(0.2)
Injury	57	(1.4)	6	(1.0)
Dyspepsia	56	(1.4)	5	(0.9)
Pneumonia	54	(1.3)	3	(0.5)
Upper Respiratory Tract Infection	48	(1.2)	1	(0.2)
Pharyngitis	44	(1.1)	3	(0.5)
Dizziness	42	(1.0)	10	(1.7)
Rash	41	(1.0)	9	(1.5)
Myalgia	34	(0.8)	6	(1.0)
Vaginitis	32	(0.8)	12	(2.1)
Sinusitis	31	(0.7)	8	(1.4)
Infection Fungal	29	(0.7)	10	(1.7)
Moniliasis	26	(0.6)	3	(0.5)
Back Pain	24	(0.6)	11	(1.9)
Fatigue	24	(0.6)	7	(1.2)
Pruritus Genital	21	(0.5)	7	(1.2)
Pain	21	(0.5)	6	(1.0)
Urinary Tract Infection	11	(0.3)	6	(1.0)

Applicant's Conclusions

- Augmentin XR was generally well-tolerated in controlled and uncontrolled clinical studies. The adverse event profile of Augmentin XR in all exposed patients was similar across the controlled and uncontrolled clinical studies.

- There were no clinically significant issues identified in the new safety data from Studies 547, 557 and 592 when compared to the safety data from the original NDA. The overall adverse event profiles of Augmentin XR were similar in the NDA, new and combined datasets among all exposed, controlled study and uncontrolled study patients.

- The adverse event profile of Augmentin XR was similar to that of Augmentin 875/125 mg b.i.d. in a direct comparison of the two treatments in Study 546, including gastrointestinal AEs, the body system with the most frequently reported AEs in either treatment group.

- Diarrhea (17.4%) was the only adverse event reported by ≥5% of Augmentin XR-treated patients (all exposed) in the Phase 3 clinical studies. Diarrhea was also the most frequently reported AE for patients in the controlled studies (Augmentin XR: 19.8%, All Comparators 9.9%). Overall, diarrhea required corrective treatment for 4.0% of Augmentin XR-treated patients (all exposed). In controlled studies, 4.9% of Augmentin XR and 2.4% of All Comparator-treated patients required corrective therapy for diarrhea. Diarrhea necessitated premature study withdrawal for 0.8% of all exposed Augmentin XR patients. In Study 546 (head to head comparison of Augmentin XR to Augmentin 875/125mg bid), diarrhea was reported in 18.0% of patients in the Augmentin XR group and in 14.3% of patients in the Augmentin 875/125mg group; the difference between the treatment groups was not statistically significant (P=0.28; 95% CI= -2.6%,10.1%).

Deaths

Summary

In the Augmentin XR Phase 3 clinical program, 28 patients in 9 studies had serious adverse experiences (SAEs) associated with death that were reported in the clinical study database. Among patients who received Augmentin XR, SAEs reported on-therapy to within 30 days post-therapy that were associated with death were reported in 26/4144 patients, including 5 patients who participated in controlled community acquired pneumonia (CAP) studies and 21 patients who participated in uncontrolled CAP studies. Of these 26 patients, 3 patients died on-therapy, 19 patients died within 30 days post-therapy and four patients died more than 30 days post-therapy. In addition, an SAE that occurred more than 30 days post-therapy was associated with death in one patient who received Augmentin XR. Among the 1387 patients who received a comparator medication, an SAE reported on-therapy to within 30 days post therapy was associated with death in a single patient who received Augmentin 875/125mg b.i.d. in Study 546.

Due to the higher rate of morbidity and mortality associated with CAP compared with acute bacterial sinusitis (ABS) or [redacted], it is not unexpected that all of the deaths within 30 days post-therapy in this clinical program were in CAP patients.

Serious AEs associated with death were primarily associated with the cardiovascular, vascular (extracardiac), and respiratory body systems. All SAEs associated with death were considered by the investigators to be unrelated or unlikely to be related to the study medication and most likely due to worsening of the condition under study or pre-existing medical conditions.

Deaths in three additional patients that occurred more than 30 days post-therapy were associated with SAEs (aggravation of pneumonia, pulmonary carcinoma, and respiratory insufficiency/pulmonary edema) reported on-therapy to within 30 days post-therapy; one patient received Augmentin XR in CAP Study 556 and two patients received Augmentin XR in [redacted] Study 549. The outcome of death in these patients was not known until some time after study completion; therefore, they were not reported in the clinical study database and are not included in the ISS SAS datasets.

Table 13: Number (%) of Patients Reporting Serious Adverse Experiences On-Therapy or within 30 days Post-Therapy Associated with Death (All Patients Exposed to Study Medication)

	Augmentin XR N= 4144		All Comparators N=1387	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one SAE associated with death	26	(0.6)	1	(0.1)
Pulmonary Carcinoma	4*	(0.1)	0	
Cardiac Arrest	3	(0.1)	1	(0.1)
Cardiac Failure	3	(0.1)	0	
Embolism Pulmonary	3	(0.1)	0	
Pneumonia	3	(0.1)	0	
Cerebrovascular Disorder	2	(<0.1)	0	
Myocardial Infarction	2	(<0.1)	0	
Neoplasm (NOS)	2*	(<0.1)	0	
Cardiac Failure (left)	1	(<0.1)	0	
Cardiomyopathy	1	(<0.1)	0	
Death (NOS)	1	(<0.1)	0	
Infection TBC (tuberculosis)	1	(<0.1)	0	
Myocarditis	1	(<0.1)	0	
Renal Failure Acute	1*	(<0.1)	0	
Respiratory Disorder	1	(<0.1)	0	
Respiratory insufficiency	1	(<0.1)	0	

* Four patients died more than 30 days post-therapy although the onset of SAEs associated with death occurred during the interval on-therapy to within 30 days post-therapy: patients 546.104.13872 and 547.249.08678 (pulmonary carcinoma), patient 547.110.06991 (renal failure acute), and patient 547.191.06385 (neoplasm NOS).

Since deaths occurred with greater frequency in the Augmentin XR arm, Dr. Thamban Valappil (Biostatistician) looked at the baseline characteristics in these patients. (Table 14 below)

Table 14: Demographic Characteristics (Patients Reporting Serious Adverse Experiences Associated with Death)

Demographic Characteristic	Treatment Group Augmentin XR 2000/125mg bid N=26	
Gender n (%)		
Male	17	(65.4%)
Female	9	(34.6%)
Age (year)		
<65 years	5	(19.2%)
65-75 years	14	(53.8%)
>75	7	(26.9%)
Mean (SD)	69.5	(12.5)
Median	70.5	
Race n (%)		
White	16	(61.5)
Black	1	(3.8)
Other	9	(34.6)
Comorbidities[a]		
Cardiac Disease	11	
Pulmonary Disease	8	
Hepatic Disease	0	
Immuno-suppressive	1	
Renal Disease	3	
PRSP	0	

[a] The same subject could have more than one co-morbidity conditions

Medical Officer's Comments:

The mean age of patients who died was 69.5 years, and almost all of these patients had comorbidities, i.e. cardiac disease, pulmonary disease, renal disease etc. None of these patients had resistant pathogens isolated, and none of them had hepatic dysfunction.

Detailed Narratives of deaths are presented below. There were **6 deaths in the controlled studies – 5 in the Augmentin XR group and one in the comparator group.**

Patient Narratives for Deaths in the Augmentin XR Group – Controlled Studies

- A 71-year-old male (Patient ID #546.026.00014) had a medical history that included coronary artery disease (triple bypass surgery), diabetes, and amputation below right knee. He was on several concomitant medications for his diabetes and heart condition. The patient began treatment on 22 November 1999. The next day, he reported trouble sleeping the night before due to shortness of breath. Later on that same morning he was found unresponsive on the floor. The cause of death was reported as myocardial infarction.

Medical Officer's Comments:

- *This patient died while he was **on therapy** with Augmentin XR. His fatal myocardial infarction is unlikely to be associated with his therapy and probably associated with the patient's history of coronary artery disease.*

- A 45-year-old male (Patient ID #556.062.02572) had a medical history that included alcohol abuse with psychiatric disease. He received Augmentin XR for 6 days. Death occurred one day after stopping therapy from a cerebral vascular accident. An autopsy was not performed.

Medical Officer's Comments:

- *This patient's death occurred **one day after the last dose of Augmentin XR**. The case-report form was reviewed and no additional information was provided. There have not been published reports associating CVA with any other marketed Augmentin formulations, so it is unlikely that this cerebral vascular accident was related to treatment with Augmentin XR.*

- A 79-year-old male (Patient ID #546.104.13872) received Augmentin XR for 7 days for CAP. His medical history included heart disease, hypertension, femoral bypass, colonectomy, benign prostrate hyperplasia and multiple other disorders. On day 23 post-therapy, he was diagnosed with squamous cell carcinoma and on day 82 post-treatment, he died.

- A 77-year-old male, (Patient ID #546.220.00790) had a medical history that included coronary artery disease, left bundle branch block, renal insufficiency and a previous myocardial infarction. On day 5 of therapy, the patient experienced adynamia with cough and dyspnea on exertion. The patient was hospitalized and continued therapy as per protocol. Eight days post-therapy, the patient died from left ventricular failure. An autopsy was not performed.

- An 85-year-old male (Patient ID #556.302.03152) whose medical history included tuberculosis received Augmentin XR as per protocol. Three days after the last dose, his condition had not improved. He had fever, loss of appetite and continued sputum production. He continued to worsen and on day 9 post-therapy, his dyspnea intensified and he died. An autopsy was not performed, but the investigator suspected neoplasm of the left lung.

Medical Officer's Comments:

Patients 546.104.13872, 546.220.00790, and 556.302.03152 were all more than 70 years old, had comorbid conditions present with CAP, and died either from their underlying disease or from development of pulmonary neoplasms.

Patient Narrative for Death in the Augmentin 7:1 Group – Controlled Study

- A 66-year-old male (Patient ID #546.021.00042) enrolled in the controlled CAP whose medical history included erectile dysfunction and numbness of right foot. The

patient's condition worsened after 4 days on treatment, and patient was withdrawn from the study. He was referred to a pulmonologist who ordered a CT Scan and biopsy was performed. Three days after therapy was stopped, the patient was diagnosed with small cell carcinoma of the right lung. The patient suffered a cardiac arrest and died 27 days post-treatment.

Medical Officer's Comments:

This patient's death was unlikely to be related to treatment with Augmentin 7:1. The cause of death was small cell carcinoma of the lung.

There were **21 deaths in the uncontrolled CAP study 547.**

Patient Narratives for Deaths in the Augmentin XR Group – Uncontrolled Study

- A 75-year-old female (Patient ID #010.08395) had a medical history that included asthma, peptic ulcer disease, gastritis, and congestive heart failure. She was on several concomitant medications. She received Augmentin XR for 8 days. On the second day into the study, she has increased mucous secretions and then developed bronchospasm on the following day. Two days post-treatment, she experienced ventilatory failure and was hospitalized. She required intubation and died on the same day. The cause of death was COPD and suspected pulmonary embolism.

Medical Officer's Comments:

The patient's death was unrelated to treatment with Augmentin XR. The cause of death was probably due to pulmonary thromboembolism.

- A 73-year-old female (Patient ID #010.08400) had a medical history that included hypertension, chronic obstructive lung disease and congestive heart failure. Concomitant medications included nifedipine. She received treatment for only one day. She developed congestive heart failure and was withdrawn from the study. Two days post-treatment, her condition worsened and she died.

Medical Officer's Comments:

The patient's death was unrelated to treatment with Augmentin XR. The cause of death was congestive heart failure probably associated with COPD, and suspected ischemic heart disease.

- A 92-year-old female (Patient ID #022.06914) with history of chronic bronchitis and arteriosclerosis received Augmentin XR for 7 days. The following day she experienced worsening pulmonary symptoms compatible with bronchopneumonia. On day 3 post-therapy, she died, and no autopsy was performed.

Medical Officer's Comments:

This patient's outcome was treatment failure and the cause of death was reported as bronchopneumonia probably associated with arteriosclerosis.

- A 70-year-old female (Patient ID # 050.08407) whose medical history included COPD, heart failure, dehydration, and hypernatremia, received 5 days of therapy with Augmentin XR. On day 2 of therapy, she developed severe bronchospasm and chest x-ray showed new infiltrates. She had progressive hemodynamic deterioration, required mechanical ventilation, and on day 5 of therapy, died. The last bronchial sample showed acid fast bacilli.

Medical Officer's Comments:

*The patient's death occurred **on therapy** with Augmentin XR. The apparent cause of death was pulmonary tuberculosis.*

- A 69-year-old male (Patient ID #070.06709) had a medical history that included diabetes mellitus, ischemic heart disease and uncontrolled hypertension. On day 3 of treatment, he suffered a cerebral vascular accident, and became comatose. Treatment with Augmentin XR was stopped. The patient never regained consciousness and on day 6 post-therapy, he died.

Medical Officer's Comments:

The patient's death was unrelated to treatment with Augmentin XR. The cause of death was cerebral vascular accident.

- A 71-year-old male (Patient ID #173.06897) had a medical history that included diarrhea, anemia, atrial fibrillation and hypoproteinemia. He received 4 days of therapy, and was not improving on therapy. Chest-x-ray revealed lung congestion. He was treated appropriately for his lung congestion but did not respond to therapy. Death occurred two days after the last dose.

Medical Officer's Comments:

The patient's death was unrelated to treatment with Augmentin XR. The cause of death was lung congestion probably associated with hypoproteinemia.

- An 80-year-old male (Patient ID #175.06362) diagnosed with diabetes mellitus; dehydration and coronary artery disease at screening received 4 days of Augmentin XR. On day 5, he became hypoglycemic probably related to gliclazide. One day after the last dose, the patient suddenly became cyanotic, had suddenly increased tachypnea, experienced shock and cardiac arrest. Blood pressure was undetermined. An electrocardiogram showed asystole. The patient was treated with Dexamethasone. Resuscitation was ineffective. The clinical outcome at the end of therapy was 'unable to determine'. The patient died on the same day from a pulmonary embolism. An autopsy was not performed.

Medical Officer's Comments:

The patient's death was unrelated to treatment with Augmentin XR. The cause of death was pulmonary embolism secondary to the underlying diabetes mellitus.

Medical Officer's Comments:

The following fourteen patients' deaths were unrelated to treatment with Augmentin XR, but were due to either the underlying medical conditions such as HIV infection, cardiovascular disease, renal disease or development of neoplasm. All of these deaths occurred post-treatment with Augmentin XR.

- A 70-year-old male (Patient ID # 010.08394) had a medical history that included congestive heart failure, hypertension, diabetes mellitus, diabetic retinopathy, limb amputation and systemic atherosclerosis. At baseline he had elevated serum creatinine of 4.4 mg/dL (normal 0.5-1.4 mg/dL), with a low creatinine clearance at 13 ml/min. (normal>30 ml/min.). He was on several concomitant medications. He received Augmentin XR for 6 days and was withdrawn from the study because of abnormal renal function. He was hospitalized, and his renal function deteriorated. Eleven days post-treatment, he died. Prior to his death, he exhibited signs of uremic encephalopathy.

- This death occurred in a 62-year-old female (Patient ID #053.08430) whose medical history included rheumatoid arthritis, anemia, peripheral vascular ischemia and gastritis. She was on several concomitant medications including methotrexate. She received Augmentin XR for 6 days, but with no improvement. She was classified as clinical failure and was given vancomycin and metronidazole. She went into septic shock and developed adult respiratory distress syndrome (ARDS). She died on day 16 of post-therapy due to worsening of CAP.

Medical Officer's Comments:

Although classified as treatment failure of Augmentin XR, it is likely that her presenting symptoms were due to ARDS. ARDS was possibly related to treatment with methotrexate.

- A 60-year-old female (Patient ID #070.06705) with history of diabetes mellitus received Augmentin XR for 7 days. Initially, the patient's condition improved but she developed pleural fluid, was classified as failure and treated with an unspecific antibiotic. While in the hospital, she was diagnosed with uncontrolled diabetes mellitus. The patient discharged herself from the hospital against medical advice. Twelve days post-treatment, she died of unknown cause, and no autopsy was performed.

- A 68-year-old female (Patient ID #083.06417) had a medical history that included ischemic heart disease and non-insulin dependent diabetes mellitus. She was on several concomitant medications. She took Augmentin XR for 6 days. Four days post-therapy, she developed supraventricular arrhythmia and was treated with verapamil hydrochloride. The same day, she had acute heart failure and died.

- This death occurred in a 68-year-old male (Patient ID #110.06911) whose medical history included previous right nephrectomy and splenectomy following abdominal trauma in 1977. Concomitant medications included Aspirin (acetylsalicylic acid), indomethacin and pilocarpine. The patient received oral study medication,

amoxicillin trihydrate/clavulanate potassium, from 28 July 2000 at dose 2000/125 mg twice daily. The following screening laboratory parameters measuring renal function were reviewed: urea measured 8.1 mmol/L (normal range 2.5-10.5), creatinine 99micromol/L (normal range 44-124) and white cell count 19,600 cell/mm^3. On 28 July 2000, urinalysis revealed 3+ blood, 1+ protein, 50-100 red blood cells/hpf and 3-5 hyaline casts. At this time the investigator suspected that the abnormal urinalysis was attributable to pneumonia, but retrospectively, the investigator considered that the patient could have had a rapidly progressing glomerulonephritis. On 31 July 2000, urinalysis was repeated and revealed 2+ blood, 1+ protein and 25-50 red blood cells/hpf. The patient completed treatment with study medication on 03 August 2000. The clinical outcome at the end of therapy visit was success. Four days post-treatment, the patient's renal function deteriorated. The investigator suspected interstitial nephritis, although this was not confirmed, as renal biopsy was not performed. The patient was diagnosed as having acute renal failure. The patient was treated for this event with aggressive fluid treatment and unspecified steroids. The investigator reported the renal failure to be possibly related to treatment with study medication. The investigator commented that it was likely that the patient had a pre-existing renal disease such as rapidly progressive glomerulonephritis because the patient's creatinine was elevated on admission. The investigator could not exclude the possibility that the patient developed an acute interstitial nephritis associated with treatment with study medication but the patient also received indomethacin, which in the investigator's opinion could have caused acute tubular necrosis. The patient commenced cyclophosphamide and prednisone for a presumed diagnosis of vasculitis from 25 August 2000. The patient was initially reported to have died on 10 October 2000 from multiple organ failure. Death occurred 70 days after the last dose of study medication. The investigator commented that retrospectively the clinical impression was that the patient had pre-existing vasculitis such as Wegener's Granulomatosis. The preliminary findings of the autopsy were that the patient died of an overwhelming cytomegalovirus (CMV) infection. The autopsy report was subsequently reviewed again and the investigator reiterated his initial clinical opinion regarding this patient. The investigator considered that the patient had a pulmonary vasculitis. Examination of the lung revealed pulmonary hemorrhage and evidence of a vasculitis, which in the investigator's opinion was in keeping with Wegener's Granulomatosis. In view of these findings the investigator amended his assessment of the relationship between the patient's death due to renal failure and treatment with study medication from possibly related to unrelated.

Medical Officer's Comments:

Initially, this patient's nephritis was considered possibly related to treatment with Augmentin XR and/or indomethacin. However, the history is consistent with Wegener's granulomatosis and appears to be unrelated to treatment. The ultimate cause of death based on the autopsy report was due to pulmonary vasculitis due to Wegener's Granulomatosis.

- A 72-year-old female (Patient ID #117.06322) whose medical history included hypertension, weight loss and anemia received only one day of therapy and was

withdrawn from the study because of moderate diarrhea. On day 7 past-treatment, the patient died at home, from a suspected myocardial infarction. An autopsy was not performed.

- A 76-year-old female (Patient ID #123.06308) had a medical history that included hypertension and COPD. She received 7 days of treatment with no improvement, so was classified as clinical failure. Some 22 days after the last dose, the pneumonia had not resolved. She had pleural fluid analysis and lung biopsy performed, which showed undifferentiated giant cell carcinoma. On day 29 post-treatment, she died. An autopsy was not performed.

- A 68-year-old male (Patient ID #191.06385) with history of hypertension was treated with Augmentin XR for 7 days. Six days after the last dose, chest x-ray showed evidence of a shadow on the lung. He underwent a bronchoscopy, which revealed a bronchial neoplasm. On day 155 post-therapy, the patient died from his cancer.

- This death occurred in a 74-year-old male (Patient ID #231.08840) whose medical history included cardiovascular disease, carotid endarterectomy, heart attack, diabetes mellitus, hypertension and hyperlipidemia. He was on several concomitant medications at time of entry in to the study. The patient received two days of therapy, and since he did not improve was switched to levofloxacin and the clinical outcome was termed as failure. Six days post-treatment, he was admitted to the ER in cardiopulmonary arrest and died.

- A 36-year-old male (Patient ID #236.08629) with history of HIV infection and dyspnea received 8 days of therapy with Augmentin XR. Five days after the last dose of study medication, the patient presented to the emergency room with complaints of chest pain and dyspnea. He was admitted to the intensive care unit and his condition worsened. The patient went into third degree heart block and subsequently suffered from cardiac arrest. Cardiac enzyme values included creatine kinase (CK) of 450 U/L (reference range 0-230), CK-MB of 70 ng/ml (reference range 0.0-5.0), and troponin-I of 41.6 ng/ml (reference range 0.0-1.9). Resuscitation attempts were unsuccessful, and the patient died. The cause of death was reported as viral myocarditis.

- A 67-year-old male (Patient ID # 249.08678) had a medical history that included infra-renal abdominal aortic aneurysm, chronic obstructive pulmonary disease (emphysema and bronchitis), osteoarthritis, hepatic cyst, and bilateral renal cyst. Concomitant medications included hydrocodone/paracetamol (Vicodin). The patient received 7 days of therapy. Eighteen days after the last dose of therapy, he experienced severe epistaxis for which he was hospitalized. The epistaxis resolved on day 2 of hospitalization, but CT of chest revealed a 4-cm hilar mass with associated adenopathy in the subcarinal region, anterior-posterior window and anterior mediastinum. On day 33 post-treatment, the patient died due to the lung cancer.

- This death occurred in a 46-year-old male (Patient ID #371.15033) whose medical history included interstitial lung disease, mild coagulopathy, pharyngitis, dysphagia,

nutritional deficit, volume depletion with transient hypotension, tobacco and alcohol abuse, lower back pain, and right eye trauma. Concomitant medications included paracetamol/chlorphenamine maleate/phenylephrine hydrochloride (Dristan), vitamin K, and solumedrol. The patient was treated for 7 days. Eight days after the last dose, the patient complained of increased shortness of breath. The patient was seen at an emergency room. He was admitted to the hospital with a diagnosis of adenocarcinoma of the lung with cardiac tamponade. The diagnosis of adenocarcinoma was based on pericardial fluid evaluation, and metastatic adenocarcinoma was suspected.

- An 84-year-old male (Patient ID #450.18829) whose medical history included peripheral vascular disease (problems with the arteries and veins of the lower limbs), pulmonary embolism and hip prosthesis secondary to osteoarthritis of the hip received 5 days of therapy. After 5 days of study treatment, the patient was withdrawn due to an adverse event of diarrhea, which was considered unrelated to study mediation. Some 26 days after the last dose, the patient had a fatal cardiac arrest. An autopsy was not performed.

- A 73-year-old male (Patient ID #455.18591) had a medical history that included mediastinal adenopathy and chronic lymphocytic leukemia. He was on several concomitant medications. The patient received one day of therapy. The clinical outcome at the end of therapy was failure due to clinical and radiological worsening of pneumonia. On day 11 after the last dose, the patient was diagnosed with a pulmonary embolism. This diagnosis was made based on the patient's underlying disease and risk factors including the patient's chronic lymphocytic leukemia (a chest computer tomography scan showed large mediastinal nodes and compressing vessels), bed confinement and sudden deterioration. The patient died 27 days post-therapy due to the pulmonary embolism. An autopsy was not performed.

Applicant's Conclusions

- Patient deaths occurred infrequently in the Augmentin XR Phase 3 studies. All patient deaths that occurred within 30 days of the cessation of therapy were in the CAP program. Most patients who died were over age 65 and had comorbid conditions.

- All SAEs associated with death were considered by the investigators to be either unrelated or unlikely to be related to Augmentin XR or comparators.

Medical Officer's Overall Comments on Deaths in the Augmentin XR group

All the deaths were looked at in great detail. Case-report forms were reviewed, and all death narratives were summarized. The sponsor reported 26 deaths in Augmentin XR patients versus one death in a comparator patient, all CAP patients. However, the majority of deaths occurred in the non-comparative studies. In the comparative CAP trials, there were 5 deaths in Augmentin XR patients versus one death in a comparator patient, a difference that was not statistically significant. The mortality rate in CAP patients (1.5%) is consistent with the mortality rate reported for outpatients with CAP