Demography in Controlled Clinical Studies

Demographic Characteristic	Treatment Group Augmentin XR N=1199	 All Comparators N=1226
Age (years) n (%)		
≥16 - <18	2 (0.2)	2 (0.2)
≥18 - <40	197 (16.4)	202 (16.5)
≥40 - <65	622 (51.9)	662 (54.0)
≥65	378 (31.5)	360 (29.4)
≥75	155 (12.9)	145 (11.8)
Mean (SD)	55.1 (16.1)	54.6 (16.1)
Range	17 – 92	16 – 92
Gender n (%)		
Male	596 (49.7)	612 (49.9)
Female	603 (50.3)	614 (50.1)
Race n (%)		
White	1085 (90.5)	1119 (91.3)
Black	58 (4.8)	56 (4.6)
Oriental	8 (0.7)	7 (0.6)
Other*	48 (4.0)	44 (3.6)
Weight (kg)		
Mean (SD)	78.4 (21.4)	79.4 (20.5)
Median	76	75
Range**	31 – 240	28 – 181.4
Region		
United States	622 (51.9)	642 (52.4)
European countries	557 (46.5)	567 (46.2)
Other countries†	20 (1.7)	17 (1.4)

*Includes Arab, Asian, Black Half-Breed, Guyana-Indian, Half-Caste, Hispanic, Indian (Asian), Italian-American, Native American, Native-American and German, North African, Portuguese, Spanish and Undisclosed (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

Demography in Uncontrolled Clinical Studies

Demographic Characteristic	Treatment Group Augmentin XR N=1224
Age (years) n (%)	
≥16 - <18	12 (1.0)
≥18 - <40	532 (43.5)
≥40- <65	528 (43.1)
≥65	152 (12.4)
≥75	53 (4.3)
Mean (SD)	43.8 (16.2)
Range	16 – 93
Gender n (%)	
Male	583 (47.6)
Female	641 (52.4)
Race n (%)	
White	994 (81.2)
Black	71 (5.8)
Oriental	71 (5.8)
Other*	88 (7.2)
Weight (kg)	
Mean (SD)	76 (19.3)
Median	74
Range	26 – 181.8
Region	
United States	590 (48.2)
European countries	490 (40.0)
Other countries**	144 (11.8)

*Includes Cuban, Hispanic, Indian (India), Mixed, Native American and Pakistanian (ISS SAS Datasets)

**Includes South Africa, China, Thailand, Mexico, Costa Rica, Philippines and Turkey

Among patients receiving Augmentin XR in the controlled and uncontrolled studies, 25.2% were treated for — 33.0% for CAP and 41.9% 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 59 years for — , 52 years for CAP, and 41 years for ABS. The majority of patients were white for each indication.

Adverse Experiences

Summary

The adverse experience profile of Augmentin XR has been reviewed in 59 subjects from three complete clinical pharmacology studies in 182 subject sessions. Fifty-five of the subjects received Augmentin XR. Of these, 20 subjects received Augmentin XR in combination with Maalox® Antacid and a further 12 subjects received other formulations of Augmentin (formulations varied and included existing Augmentin and Amoxil tablets). The most frequently reported AEs in all subjects were headache, diarrhea and genital moniliasis. The majority of AEs in the overall population were considered to be related to study medication and were mild in severity. No severe AEs were reported in any of the three clinical pharmacology studies.

In the Phase III controlled studies, 51.0% of patients in the Augmentin XR group reported AEs during the on-therapy and within 30 days post-therapy interval which was similar to the All Comparators group (50.4%). Also similar was the proportion of patients reporting severe AEs in the Augmentin XR and All Comparators groups (7.7% and 9.0%, respectively) as well as the proportion of patients reporting AEs of suspected/probable relationship to study medication (28.7% and 23.9%). Diarrhea was the most frequently reported AE in both the Augmentin XR and All Comparators group (17.9% and 8.1%, respectively). Nausea, the second most common AE, was reported by 3.1% of patients in the Augmentin XR group and 4.5% of patients in the All Comparators group. Severe diarrhea occurred in a small proportion of patients and with similar frequency in the Augmentin XR group and the All Comparators group (1.4% vs 0.9%, respectively). Severe nausea also occurred in a small proportion of patients in each treatment group (0.5% and 0.6%, respectively).

In the Phase III uncontrolled studies, 44.9% of patients receiving Augmentin XR reported AEs; 5.6% of patients overall reported AEs considered to be severe. The most frequently reported AEs were diarrhea, nausea and headache. The AE profile of Augmentin XR was similar to that of the combined controlled clinical studies.

The AE profile of Augmentin XR was similar to that of Augmentin 875/125mg b.i.d. 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 rate of diarrhea in the Augmentin XR arm as compared with the Augmentin 875/125mg treatment arm, although this did not reach statistical significance. The AE profile of Augmentin XR also was similar to levofloxacin and clarithromycin with the exception of the occurrences of diarrhea and genital moniliasis, which were both more prevalent in the Augmentin XR group, and taste perversion which was more prevalent in the clarithromycin group.

Methodology

For clinical pharmacology studies, an AE was defined as any experience occurring for the first time after the first dose of study medication or an experience that became more severe as compared to baseline. AEs in the post-therapy interval were collected up to 30 days after the last dose. The frequency of AEs was calculated by dosing session and not by subject. Each study had more than one dosing session per subject depending on the study design. For example, in a two-way crossover design, there were two dosing sessions and a subject who received Augmentin XR alone in one dosing session and Augmentin XR plus another drug in the other dosing session would appear in both the Augmentin XR and Augmentin XR + Other dosing sessions. Several AEs may have been reported by one subject in any one dosing session but if the same AE occurred more than once in a dosing session it was only counted once. If a subject reported the same AE in two different dosing sessions, it was counted twice – once in each of the two respective dosing sessions. In clinical pharmacology studies, all AEs considered by the investigator to be of probable, suspected (reasonable possibility), or unlikely relationship to study medication were combined as "related" for the analysis by relationship to study medication. This conservative approach was taken in order to ensure that any AEs which could possibly be related to the study drug, no matter how remotely, were grouped and classified as related for the healthy subjects participating in the Phase I clinical pharmacology studies. Unrelated AEs were tabulated separately.

In the Phase III clinical program, AEs were defined as events that had a time to onset occurring after the first dose of study medication. All AEs were coded from the verbatim term according to the World Health Organization Adverse Reaction Terminology (WHO-ART) coding dictionary by mapping to the preferred term and body system.

Adverse experiences were elicited by the investigator asking the patient the non-leading question as stated in the protocol *"Do you feel differently in any way since starting the new treatment?"* If the patient responded *"Yes"*, details of the AE were documented on the Case Report Form such as its severity, outcome status, investigator attribution to study medication, any corrective therapy given and any change in study medication administration. The same methodology for soliciting AEs was used in the Phase I studies, however, in the Phase III clinical studies, "related" AEs included those considered by the investigator to be of suspected (reasonable possibility) or probable relationship. AEs of unlikely relationship to study medication were grouped with unrelated AEs.

In deriving the AE frequency calculation(s), the number of patients with at least one AE were counted and not the number of AEs. That is, if a patient reported three occurrences of the same AE within a time interval, the AE was counted only once. If a patient reported more than one AE, which in turn mapped to an identical WHO-ART body system, the AE was counted once in the total number of AEs for that body system.

The safety population included all randomized patients who took at least one dose of study medication. Adverse experience tables were produced for the following three patient populations: all patients in controlled clinical studies, all patients in uncontrolled clinical studies and all patients exposed to either Augmentin XR or comparator. For each of these three populations, the following sets of AE tables were produced:

- All AEs
- AEs by relationship to study medication (includes AEs of probable or suspected relationship)
- AEs by severity (mild, moderate, or severe)

Within each set of tables, AEs are summarized by body system and preferred term classification according to the following time intervals:

- On-therapy: All AEs that started after first dose of medication, up to and including AEs that started on the last day of study medication.
- On-therapy and within 30 days post-therapy: All AEs that started after the first dose of medication, up to and including AEs that started within 30 days after the last day of study medication.
- After 30 days post-therapy: All AEs that started more than 30 days after the last day of study medication.

Data analysis using inferential testing for statistical significance was performed for the number of patients reporting AEs occurring at a frequency of ≥5% in any treatment group for the on-therapy and on-therapy and within 30 days post-therapy time intervals in the controlled studies. The Mantel-Haenszel chi-square test stratified by study, was used to calculate 95% confidence intervals and P-values. Additionally, AEs that were reported to be significant in ≥5% of patients in the comparator studies were analyzed for statistical significance. This included Study 548 where the inferential analysis between treatment groups consisted of the Fisher's exact test and two-sided 95% confidence intervals using the normal approximation to the binomial distribution.

Clinical Pharmacology

A total of 59 subjects were enrolled in three Clinical Pharmacology studies (Study 553, Study 558, and Study 583) comprising 182 subject dosing sessions. All three studies were open, randomized, single dose, crossover studies. All subjects may have received (A) one or more single doses of Augmentin XR either alone or in combination with another drug or (B) another formulation of Augmentin. A total of 55 subjects received Augmentin XR at one or more dosing sessions (Study 558, 8 subjects; Study 553, 27 subjects; Study 583, 20 subjects). Twelve subjects were enrolled in Study 558. All twelve of these subjects received other formulations of Augmentin which were not progressed to Phase III studies. Of these twelve subjects, eight subjects also received Augmentin XR in a crossover design. Twenty-seven subjects were enrolled in Study 553, all of which received Augmentin XR. Each of the twenty subjects enrolled in Study 583 received Augmentin XR alone and in combination with Maalox® Antacid.

The frequency of reporting of AEs during subject dosing sessions was: Augmentin XR alone (40.7%), Augmentin other formulations (36.1%); Augmentin XR + Maalox (28.9%) and combined populations (37.4%). Overall, the most frequently reported AEs in all subject dosing sessions were headache (15.4%), diarrhea (4.4%), genital moniliasis (3.8%), nausea (2.2%), upper respiratory tract infection (2.2%), and pain (2.2%). These AEs were also the most common AEs reported during subject sessions in the Augmentin XR alone group.

In the total study population, 71.3% (57/80) of all AEs were considered to be "related" (includes: probable, suspected and unlikely relationships) to the study medication. The majority, 70% (35/50) of all AEs reported in subjects who received Augmentin XR alone were considered to be related to st udy medication. Eighty-two percent (14/17) of the AEs reported in subjects who received Augmentin other formulations were considered to be related to study medication while 61.5% (8/13) of AEs reported in subjects who received Augmentin XR + Maalox were considered to be related to study medication.

The majority of AEs were mild in severity (71.0%). No AE was identified to be severe. In general, the severity of AEs was similar across all treatment groups.

Clinical Studies

The clinical study data are grouped and summarized in this section by controlled clinical studies (Study 546, Study 548, Study 549, Study 550, Study 556) and uncontrolled clinical studies (Study 547, Study 551). Additional analyses include comparison to Augmentin 875/125mg b.i.d. (Study 546), comparison to levofloxacin (Study 549 and Study 550 data combined) and comparison to clarithromycin (Study 548). In all clinical studies, Augmentin XR was administered at a dose of 2000/125mg b.i.d..

Controlled Studies

The controlled 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, and one ABS study (Study 550) with a treatment duration of 10 days.

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

Most Frequent Adverse Experiences by Body System

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 the All Comparators group (50.1% and 48.8%, respectively).

The body system with the greatest proportion of AEs was the gastrointestinal system where 29.1% of patients in the Augmentin XR group and 22.7% in the All Comparators group reported at least one AE. The proportion of patients that experienced respiratory AEs was similar between the Augmentin XR group and the All Comparators group (9.5% vs 10.7%, respectively). Adverse experiences pertaining to resistance mechanism, which includes infections presumed to be the result of an imbalance of the protective normal flora causing an overgrowth of pathogenic bacteria, occurred in 9.2% of patients in the Augmentin XR group and 5.7% of patients in the All Comparators group. The proportion of patients reporting central and peripheral nervous system AEs was lower in the Phase III clinical studies than in the clinical pharmacology studies and also was similar to that of the phase III All Comparators groups.

The number (%) of patients with the most frequently (≥5% in either treatment group) reported AEs by body system are summarized in the following table.

Number (%) of Patients Reporting Adverse Experiences (≥5% in Either Treatment Group) by Body System in Controlled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226	
Body System	n	(%)	n	(%)
Patients with at least one AE	612	(51.0)	618	(50.4)
Gastrointestinal	349	(29.1)	278	(22.7)
Respiratory	114	(9.5)	131	(10.7)
Resistance Mechanism	110	(9.2)	70	(5.7)
Body as a Whole	82	(6.8)	87	(7.1)
Central and Peripheral Nervous	69	(5.8)	78	(6.4)

Most Frequent Adverse Experiences by Preferred Term

During the interval on therapy and within 30 days post-therapy, similar proportions of patients in each treatment group (approximately 50%) reported at least one AE. The most frequently reported AE in both treatment groups was diarrhea, which occurred in a greater proportion of patients in the Augmentin XR group than in the All Comparators group (20.0% and 9.3% respectively; P<0.01). Diarrhea required corrective treatment for 5.1% of patients in the Augmentin XR group and for 2.2% of patients in the All Comparators group.

Nausea, the second most frequently reported AE in both treatment groups, occurred with similar frequency for the Augmentin XR and All Comparators groups (4.8% and 5.6%, respectively; P=0.43).

Additionally, two AEs were analyzed for statistical significance between treatment groups in the all controlled studies because these AEs reached significance in ≥5% of patients in comparator Study 548. In the combined controlled studies, genital moniliasis (candidiasis) occurred in 2.6% of Augmentin XR recipients and in 0.7% of patients in the All Comparators group (P<0.01); taste perversion occurred in 0.5% of Augmentin XR recipients and in 3.1% of patients in the All Comparators group (P<0.01).

Number(%) of Patients With the Most Frequently Occurring (≥1% in Either Treatment Group) Adverse Experiences by Preferred Term in Controlled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226	
Preferred Term	n	(%)	n	(%)
Patients with at least one AE	612	(51.0)	618	(50.4)
Diarrhea	240	(20.0)	114	(9.3)
Nausea	58	(4.8)	69	(5.6)
Headache	45	(3.8)	42*	(3.4)
Moniliasis Genital (Candidiasis)	31	(2.6)**	8	(0.7)
Abdominal Pain	29	(2.4)	40	(3.3)
Rhinitis	24	(2.0)	29	(2.4)
Insomnia	22	(1.8)	23	(1.9)
Vomiting	21	(1.8)	21	(1.7)
Infection Viral	19	(1.6)	10	(0.8)
Upper Respiratory Tract Infection	19	(1.6)	7	(0.6)
Injury	17	(1.4)	24	(2.0)
Pharyngitis	15	(1.3)	20	(1.6)
Sinusitis	15	(1.3)	20	(1.6)
Dyspepsia	15	(1.3)	13	(1.1)
Moniliasis	15	(1.3)	13	(1.1)
Infection Fungal	15	(1.3)	10	(0.8)
Bronchitis	13	(1.1)	14	(1.1)
Constipation	13	(1.1)	13	(1.1)
Rash	13	(1.1)	12	(1.0)
Chest Pain	13	(1.1)	9	(0.7)
Fatigue	12	(1.0)	11	(0.9)
Myalgia	11	(0.9)	13	(1.1)
Dizziness	10	(0.8)	15	(1.2)
Back Pain	9	(0.8)	20	(1.6)
Mouth Dry	9	(0.8)	15	(1.2)
Flatulence	8	(0.7)	15	(1.2)
Taste Perversion	6	(0.5)	38	(3.1)

*This number excludes one patient (546.118.00363) treated with Augmentin 875/125mg who had a baseline AE of headache which was mistakenly included in the on-therapy time interval in Study 546.

** The percentage rate of candidal moniliasis listed here is based on the total population. If this rate were determined based on the total number of female patients, it would be approximately double what is listed in this table. The percentages of male to females in the controlled trials is 50.5 % male vs. 49.5% female.

The frequency of AEs for patients taking Augmentin XR in the controlled studies is similar to the frequency of AEs for patients taking Augmentin XR in the combined controlled and uncontrolled studies.

The following table summarizes selected adverse events on therapy and within 30 days post therapy for individual comparators in all Controlled Clinical Trials.

Number (%) of Patients with Diarrhea and Moniliasis in ALL Controlled Clinical Studies of NDA 50-785 (On therapy and Within 30 days post therapy)

	Treatment Group											
	Augmentin XR (16:1) N=1280		All Comparators N=1308		Augmentin 875 (7:1) N=259		Augmentin 1gr N=175		Levo-floxacin N=497		Clarithro-mycin N=295	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with at least one AE	641	(50.1)	638	(48.8)	133	(51.4)	94	(53.7)	212	(38.1)	199	(62.6)
Diarrhea	256	(20.0)	120	(9.2)	37	(14.3)ψ	17	(9.7)	32	(5.8)	34	(10.7)
Moniliasis Genital**	31	(2.6)	8	(0.7)	3	(1.2)ψ	0*	(0)	3	(0.6)	2	(0.7)

* There were no cases of genital moniliasis in this study in either treatment arm (Augmentin XR or Augmentin 1gr)

ψ The rates of diarrhea and genital moniliasis in this study for Augmentin XR were 18.0% and 1.2%.

** The percentage rate of candidal moniliasis listed here is based on the total population. If this rate were determined based on the total number of female patients, it would be approximately double what is listed in this table. The percentages of male to females in the controlled trials is 50.5 % male vs. 49.5% female.

Adverse Experiences by Relationship to Study Medication

At least one AE was considered to be of suspected or probable relationship to study medication for 28.7% of patients in the Augmentin XR group and 23.9% of patients in the All Comparators group. The most frequent AEs of suspected or probable relationship to study medication in the Augmentin XR group were diarrhea (17.9%), nausea (3.1%) and genital moniliasis (2.5%). The most frequent AEs of suspected or probable relationship to study medication in the All Comparators group were diarrhea (8.1%), nausea (4.5%), taste perversion (2.9%) and abdominal pain (2.2%).

Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences of Suspected/Probable Relationship to Study Medication in Controlled Clinical Studies (in Either Treatment Group On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226	
Preferred Term	n	(%)	n	(%)
Patients with at least one AE of suspected/probable relationship to study medication	344	(28.7)	293	(23.9)
Diarrhea	215	(17.9)	99	(8.1)
Nausea	37	(3.1)	55	(4.5)
Moniliasis Genital (Candidiasis)*	30	(2.5)	8	(0.7)
Abdominal Pain	17	(1.4)	27	(2.2)
Moniliasis	15	(1.3)	8	(0.7)
Infection Fungal	15	(1.3)	7	(0.6)
Dyspepsia	9	(0.8)	13	(1.1)
Flatulence	7	(0.6)	12	(1.0)
Taste Perversion	6	(0.5)	35	(2.9)
Vomiting	6	(0.5)	12	(1.0)

* The percentage rate of candidal moniliasis listed here is based on the total population. If this rate were determined based on the total number of female patients, it would be approximately double what is listed in this table. The percentages of male to females in the controlled trials is 50.5 % male vs. 49.5% female.

Adverse Experiences by Severity

Most AEs were mild or moderate in severity. The proportion of severe AEs was similar between the Augmentin XR (7.7%) and the All Comparators (9.0%) groups. The most frequently reported severe AEs for patients in the Augmentin XR group were diarrhea (1.4%) and nausea (0.5%). The rates of severe diarrhea and nausea were 1.4% and 0.5% in the Augmentin group and 0.9% and 0.6% in the comparator group, respectively.

Number (%) of Patients With at Least One Adverse Experience, by Severity in Controlled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226	
Severity of AE	n	(%)	n	(%)
Mild	405	(33.8)	392	(32.0)
Moderate	317	(26.4)	325	(26.5)
Severe	92	(7.7)	110	(9.0)

Adverse Experiences by Time of First Occurrence

In general, first onset of diarrhea occurred Day 1 through Day 3 for patients in both treatment groups. For Augmentin XR-treated patients reporting diarrhea, the time to first occurrence was greatest during Day 2 (6.2%). Diarrhea occurred less frequently post-therapy where at most 0.5% of patients first experienced diarrhea on any given day post-therapy.

First onset of nausea also typically occurred from Day 1 through Day 3. For Augmentin XR recipients reporting nausea, the time to first occurrence was greatest during Day 2 (1.2%). Nausea occurred less

frequently post-therapy, where at most <1% of patients first experienced nausea on any given day post-therapy.

For the combined controlled studies, diarrhea is summarized by time of first occurrence for both the on-therapy interval and the post-therapy interval.

Number (%) of Patients With Diarrhea by Time of First Occurrence

Interval	On-Therapy				Post-Therapy			
Treatment Group	Augmentin XR		All Comparators		Augmentin XR		All Comparators	
Total Number of Patients	N=1199		N=1226		N=1199		N=1226	
Number (%) Reporting Diarrhea	225	(18.8)	106	(8.6)	20	(1.7)	9	(0.7)
Day	n	(%)	n	(%)	n	(%)	n	(%)
Day 1	48	(4.0)	20	(1.6)	6	(0.5)	2	(0.2)
Day 2	74	(6.2)	35	(2.9)	2	(0.2)	2	(0.2)
Day 3	58	(4.9)	26	(2.2)	0		2	(0.2)
Day 4	17	(1.5)	12	(1.0)	2	(0.2)	1	(0.1)
Day 5	7	(0.6)	8	(0.7)	1	(0.1)	0	
Day 6	7	(0.6)	3	(0.3)	2	(0.2)	0	
Day 7	7	(0.6)	1	(0.1)	1	(0.1)	2	(0.2)
Day>7	7	(0.6)	1	(0.1)	6	(0.5)	0	
Day 8	4	(0.6)	1	(0.1)				
Day 9	2	(0.6)	0					
Day 10	0		0					
Day >10	1	(0.5)	0					

Uncontrolled Studies

The uncontrolled studies consisted of one CAP study (Study 547) with a treatment duration of 7 days and one ABS study (Study 551) with a treatment duration of 10 days.

Most Frequent Adverse Experiences by Body System

A total of 44.9% of patients in the Augmentin XR uncontrolled studies 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 (26.1%).

Number (%) of Patients Reporting Most Frequent Adverse Experiences (≥5%) by Body System in Uncontrolled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group	
	Augmentin XR	
	N=1224	
Body System	n	(%)
Patients with at least one AE	550	(44.9)
Gastrointestinal	320	(26.1)
Central and Peripheral Nervous	75	(6.1)
Body As A Whole	67	(5.5)
Respiratory	66	(5.4)
Resistance Mechanism	62	(5.1)

Most Frequent Adverse Experiences by Preferred Term

Diarrhea was the most frequently reported AE and occurred in 17.6% of patients receiving Augmentin XR in uncontrolled studies. Diarrhea required corrective treatment for only 3.3% of patients. No other AE was reported by ≥5% of patients.

Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences by Preferred Term in Uncontrolled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group	
	Augmentin XR	
	N=1224	
Body System	n	(%)
Patients with at least one AE	550	(44.9)
Diarrhea	215	(17.6)
Headache	43	(3.5)
Nausea	41	(3.3)
Abdominal Pain	31	(2.5)
Injury	29	(2.4)
Moniliasis Genital (Candidiasis) *	23	(1.9)
Insomnia	19	(1.6)
Vomiting	19	(1.6)
Dizziness	16	(1.3)
Dyspepsia	16	(1.3)
Rash	16	(1.3)
Flatulence	15	(1.2)
Gastrointestinal Disorder NOS	15	(1.2)
Rhinitis	13	(1.1)
Epistaxis	12	(1.0)

* The percentage of genital moniliasis listed here is based on total patient population. In the uncontrolled study, there were 48% who were male, and 52% who were female. Thus, a percentage rate calculated for only the female population would result in a percentage rate of approximately double what is listed in the table above.

The most frequently occurring AE, diarrhea, was reported by 17.6% of patients in the uncontrolled clinical studies as compared to 20.0% of patients in the Augmentin XR controlled studies. The AE profile of Augmentin XR in the uncontrolled clinical studies was similar to that in the combined controlled studies.

Adverse Experiences by Relationship to Study Medication

At least one AE was considered to be of suspected or probable relationship to Augmentin XR for 26.9% of patients in the uncontrolled studies. The most frequent AEs of suspected or probable relationship to study medication were diarrhea (16.3%) and nausea (2.4%).

Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences of Suspected/Probable Relationship to Study Medication in Uncontrolled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group Augmentin XR N=1224	
Preferred Term	**n**	**(%)**
Patients with at least one AE of suspected/probable relationship to study medication	329	(26.9)
Diarrhea	199	16.3
Nausea	29	2.4
Abdominal Pain	23	1.9
Moniliasis Genital (Candidiasis)*	22	1.8
Gastrointestinal Disorder NOS	15	1.2
Flatulence	13	1.1

* The percentage of genital moniliasis listed here is based on total patient population. In the uncontrolled study, there were 48% who were male, and 52% who were female. Thus, a percentage rate calculated for only the female population would result in a percentage rate of approximately double what is listed in the table above.
NOS=not otherwise specified

Adverse Experiences by Severity

Most AEs were mild or moderate in severity. The proportion of patients with severe AEs for the Augmentin XR uncontrolled studies was 5.6% which was similar to the proportion of patients with severe AEs in the controlled studies (7.3%). The most frequently reported severe AEs in the uncontrolled studies were diarrhea (1.3%) and nausea (0.5%) which was nearly identical to the frequency of these events in the Augmentin XR group of the combined controlled studies and all patients exposed to Augmentin XR (1.4% and 0.5%, respectively).

Number (%) of Patients With at Least One Adverse Experience, by Severity in Uncontrolled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group Augmentin XR N=1224	
Severity of AE	**n**	**(%)**
Mild	394	(32.2)
Moderate	237	(19.4)
Severe*	68	(5.6)

*One patient (—547.117.06322) had both unknown and severe AEs and so is counted only once in the severe category.

Comparison With Augmentin 875/125mg

Controlled CAP Study 546 was the only study in this NDA which used the currently FDA approved Augmentin 875/125mg formulation.

Most Frequent Adverse Experiences by Preferred Term in Controlled Clinical Study 546
During the interval on-therapy and within 30 days post-therapy, similar proportions of patients in each treatment group (approximately 50%) reported at least one AE. 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 groups. However, the difference between the treatment groups was not significant (P=0.28; 95% CI= -2.6%,10.1%). No other AEs were reported by ≥5% of patients in the Augmentin XR group. Nausea was reported by a similar proportion of patients in both the Augmentin XR and Augmentin 875/125mg treatment groups (4.3% and 5.4%, respectively; P=0.68); headache was reported by a similar proportion of patients in both the Augmentin XR and Augmentin 875/125 treatment groups (4.3% and 5.0%, respectively; P=0.84). Genital moniliasis occurred in 1.2% of patients in both the Augmentin XR and Augmentin 875/125mg groups.

Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences in Either Treatment Group in Controlled Clinical Study 546 (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=255		Augmentin 875/125mg N=259	
Preferred Term	n	(%)	n	(%)
Patients with at least one AE	126	(49.4%)	133	(51.4%)
Diarrhea	46	(18.0%)	37	(14.3%)
Nausea	11	(4.3%)	14	(5.4%)
Headache	11	(4.3%)	13	(5.0%)
Rhinitis	7	(2.7%)	5	(1.9%)
Sinusitis	6	(2.4%)	5	(1.9%)
Vomiting	4	(1.6%)	7	(2.7%)
Abdominal Pain	4	(1.6%)	6	(2.3%)
Insomnia	4	(1.6%)	4	(1.5%)
Injury	4	(1.6%)	3	(1.2%)
Mouth Dry	4	(1.6%)	3	(1.2%)
Constipation	4	(1.6%)	2	(0.8%)
Dyspepsia	4	(1.6%)	2	(0.8%)
Rash	4	(1.6%)	2	(0.8%)
Upper Respiratory Tract Infection	4	(1.6%)	2	(0.8%)
Pneumonia	3	(1.2%)	4	(1.5%)
Chest Pain	3	(1.2%)	3	(1.2%)
Fatigue	3	(1.2%)	3	(1.2%)
Gastrointestinal Disorder NOS	3	(1.2%)	3	(1.2%)
Moniliasis Genital (Candidiasis)*	3	(1.2%)	3	(1.2%)
Hematuria	3	(1.2%)	2	(0.8%)
Pharyngitis	3	(1.2%)	2	(0.8%)
Pruritus Genital	3	(1.2%)	2	(0.8%)
Bronchitis	2	(0.8%)	4	(1.5%)
Dizziness	2	(0.8%)	4	(1.5%)
Pruritus	2	(0.8%)	4	(1.5%)
Anxiety	2	(0.8%)	3	(1.2%)
Neoplasm NOS	2	(0.8%)	3	(1.2%)
Edema Dependent	1	(0.4%)	4	(1.5%)
Pain	1	(0.4%)	4	(1.5%)
Pleural Effusion	1	(0.4%)	4	(1.5%)
SGPT Increased	1	(0.4%)	4	(1.5%)
Back Pain	1	(0.4%)	3	(1.2%)
Syncope	1	(0.4%)	3	(1.2%)
Anemia	0		3	(1.2%)
Cardiac Failure	0		3	(1.2%)
Therapeutic Response Increased	0		3	(1.2%)

* Percentage rate calculated based on total male and female population. The percentage of females in this study was 49.0%. Therefore, if a percentage rate were calculated for genital moniliasis using the total female population as the denominator, the percentage rate would be approximately double what is listed in the table.
NOS=not otherwise specified

Adverse Experiences by Relationship to Study Medication in Controlled Clinical Study 546

During the interval on-therapy and within 30 days post-therapy, approximately 25% of patients in each treatment group reported at least one AE of suspected or probable relationship to study medication. A comparable proportion of patients in each treatment group experienced episodes of diarrhea that were considered to be of suspected or probable relationship to study medication (Augmentin XR, 16.9%; Augmentin 875/125mg, 13.1%). The proportion of patients experiencing episodes of nausea that were considered to be of suspected or probable relationship to study medication was also similar between treatment groups (Augmentin XR, 2.7%; Augmentin 875/125mg, 4.6%).

Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences of Suspected/Probable Relationship to Study Medication in Controlled Clinical Study 546 (in Either Treatment Group On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=255		Augmentin 875/125mg N=259	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with at least one AE of suspected/ probable relationship to study medication	64	(25.1%)	64	(24.7%)
Diarrhea	43	(16.9%)	34	(13.1%)
Nausea	7	(2.7%)	12	(4.6%)
Gastrointestinal Disorder NOS	3	(1.2%)	2	(0.8%)
Moniliasis Genital (Candidiasis)*	3	(1.2%)	3	(1.2%)
Pruritus Genital	3	(1.2%)	1	(0.4%)
Abdominal Pain	2	(0.8%)	4	(1.5%)
Vomiting	1	(0.4%)	3	(1.2%)

* Percentage rate calculated based on total male and female population. The percentage of females in this study was 49.0%. Therefore, if a percentage rate were calculated for genital moniliasis using the total female population as the denominator, the percentage rate would be approximately double what is listed in the table.
NOS=not otherwise specified

Adverse Experiences by Severity in Controlled Clinical Study 546

The following table summarizes the proportion of patients experiencing at least one severe AE which was similar between the Augmentin XR and Augmentin 875/125 groups (7.8% and 7.7% respectively). The most frequently occurring severe AE was diarrhea which was reported by a small proportion of patients in the Augmentin XR and the Augmentin 875/125mg treatment groups (1.2% and 0.8%, respectively). The majority of patients reporting diarrhea indicated the AE to be of mild severity.

Number (%) of Patients with at Least One Adverse Experience, by Severity in Controlled Clinical Study 546 (On-Therapy and Within 30 Days PostTherapy)

	Treatment Group			
	Augmentin XR N=225		Augmentin 875/125mg N=259	
Severity of AE	**n**	**(%)**	**n**	**(%)**
Mild	83	(32.5%)	87	(33.6%)
Moderate	66	(25.9%)	68	(26.3%)
Severe	20	(7.8%)	20	(7.7%)

Comparison With Levofloxacin

Adverse experience data are grouped and summarized for the controlled levofloxacin comparator studies — Study 549 with 7 days of treatment; ABS Study 550 with 10 days of treatment).

Most Frequent Adverse Experiences by Body System in Levofloxacin Comparator Studies

The body system with the greatest proportion of AEs in both treatment groups was the gastrointestinal system where 26.7% of the patients in the Augmentin XR group reported gastrointestinal AEs compared to 16.5% of patients in the levofloxacin group. Adverse experiences in the respiratory system were the next most frequent. A similar proportion of patients in the Augmentin XR (6.3%) and levofloxacin (7.0%) groups reported respiratory system AEs.

Most Frequent Adverse Experiences by Preferred Term in Levofloxacin Comparator Studies

During the interval on-therapy and within 30 days post-therapy, at least one AE was reported by 44.1% of patients in the Augmentin XR group and 39.8% of patients in the levofloxacin group. The most frequently reported AEs in both the Augmentin XR and levofloxacin groups were diarrhea (Augmentin XR: 19.0%, levofloxacin: 5.2%) and nausea (Augmentin XR: 5.2%, levofloxacin: 6.0%).

The proportion of patients reporting diarrhea was greater in the Augmentin XR group than in the levofloxacin group. Notably, in Study 550 alone, the highest rate of diarrhea was reported for Augmentin XR (26.9%). Similarly, the frequency of diarrhea occurring in levofloxacin-treated patients (8.3%) was higher than for Study 549. The frequency of drug-related diarrhea for levofloxacin-treated patients was 6.5%. It is evident that both the Augmentin XR and levofloxacin treatment groups had higher diarrhea rates in Study 550 than in study 549.

Although the duration of treatment differed between Study 549 (7 days) and Study 550 (10 days), no influence on the time to first occurrence of diarrhea for Augmentin XR was noted. For Augmentin XR, the time to first diarrhea occurrence was ≤5 days in 83.3% of patients in Study 549 and 86.0% of patients in Study 550. For levofloxacin, the time to first diarrhea occurrence was ≤5 days in 78.6% of patients in Study 549 and 88.9% of patients in Study 550.

Corrective treatment for diarrhea was required by a small proportion of patients in both the Augmentin XR and levofloxacin treatment groups (4.2% and 1.3% overall, respectively).

For both the Augmentin XR and levofloxacin-treated patients, nausea was the only other AE reported by ≥5% of patients and the incidence was similar between the treatment groups (5.0% and 5.4%, respectively; P=0.75).

Number (%) of Patients With the Most Frequently Occurring (≥1% in Either Treatment Group) Adverse Experiences in Either Treatment Group in Levofloxacin Comparator Studies (Controlled Studies 549 and 550 Combined On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR		Levofloxacin 500mg	
	N=485		N=497	
Preferred Term	n	(%)	n	(%)
Patients with at least one AE	214	(44.1)	198	(39.8)
Diarrhea	92	(19.0)	26	(5.2)
Nausea	25	(5.2)	30	(6.0)
Moniliasis Genital (Candidiasis)*	12	(2.5)	3	(0.6)
Abdominal Pain	11	(2.3)	10	(2.0)
Headache	9	(1.9)	11	(2.2)
Dyspepsia	8	(1.6)	3	(0.6)
Rhinitis	7	(1.4)	10	(2.0)
Insomnia	7	(1.4)	5	(1.0)
Pharyngitis	6	(1.2)	7	(1.4)
Moniliasis	6	(1.2)	4	(0.8)
Vomiting	6	(1.2)	4	(0.8)
Bronchitis	5	(1.0)	6	(1.2)
Dizziness	5	(1.0)	5	(1.0)
Infection Viral	5	(1.0)	5	(1.0)
Cardiac Failure	5	(1.0)	0	
Back Pain	4	(0.8)	10	(2.0)
Creatine Phosphokinase Increased	4	(0.8)	5	(1.0)
Fatigue	4	(0.8)	5	(1.0)
Fungal Infection	4	(0.8)	5	(1.0)
Injury	3	(0.6)	13	(2.6)
Arthralgia	3	(0.6)	6	(1.2)
Myalgia	3	(0.6)	5	(1.0)
Mouth Dry	1	(0.2)	5	(1.0)

* The percentage rate of genital moniliasis is calculated using the total male + female populaiton. The percentage of females for studies 549 and 550 combined was 46.2%. Therefore, if the rate of moniliasis were calculated based on the female population, the percentage rate would be slightly more than double what is listed in the table above.

When the proportion of the three most frequently reported AEs in the Augmentin XR group are compared with the proportion reported by Augmentin XR-treated patients in the combined controlled studies, the frequencies are similar: diarrhea (19.0% vs. 20.0%, respectively), nausea (5.2% vs. 4.7%, respectively), and genital moniliasis (2.2% vs. 2.5%, respectively).

Adverse Experiences by Relationship to Study Medication

During the interval on-therapy and within 30 days post-therapy, 26.8% of patients in the Augmentin XR group and 18.1% of patients in the levofloxacin group reported at least one AE which the investigator considered to be of suspected or probable relationship to study medication. A greater proportion of patients in the Augmentin XR group (16.3%) reported episodes of diarrhea that were considered to be of suspected or probable relationship to study medication as compared to the proportion of patients in the levofloxacin group (4.0%). A similar proportion of patients reported episodes of nausea between the Augmentin XR and levofloxacin groups (3.1% and 4.6%, respectively). Additionally, 2.5% of Augmentin XR-treated patients experienced genital moniliasis that was considered to be of suspected or probable relationship to study medication as compared to 0.6% of patients in the levofloxacin group.

Number (%) of Patients With the Most Frequently Occurring (≥1% in Either Treatment Group) Adverse Experiences of Suspected/Probable Relationship to Study Medication in Levofloxacin Comparator Studies 549 and 550 Combined (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=485		Levofloxacin 500mg N=497	
Preferred Term	n	(%)	n	(%)
Patients with at least one AE of suspected/probable relationship to study medication	130	(26.8)	90	(18.1)
Diarrhea	79	(16.3)	20	(4.0)
Nausea	15	(3.1)	23	(4.6)
Moniliasis Genital*	12	(2.5)	3	(0.6)
Abdominal Pain	8	(1.6)	8	(1.6)
Moniliasis	6	(1.2)	2	(0.4)
Dyspepsia	5	(1.0)	3	(0.6)

* The percentage rate of genital moniliasis is calculated using the total male + female populaiton. The percentage of females for studies 549 and 550 combined was 46.2%. Therefore, if the rate of moniliasis were calculated based on the female population, the percentage rate would be slightly more than double what is listed in the table above.

Adverse Experiences by Severity

The proportion of patients experiencing severe AEs in the levofloxacin comparator studies was similar between the Augmentin XR and levofloxacin groups (7.2% and 6.4%, respectively). Most AEs, including diarrhea, were either mild or moderate in severity. An identical proportion of patients (1.1%) in the Augmentin XR and the levofloxacin groups reported episodes of severe diarrhea.

Number (%) of Patients with at Least One Adverse Experience, by Severity in Levofloxacin Comparator Controlled Studies 549 and 550 Combined (in Either Treatment Group On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=485		Levofloxacin 500mg N=497	
Severity	n	(%)	n	(%)
Mild	129	(26.6)	116	(23.3)
Moderate	114	(23.5)	109	(21.9)
Severe*	35	(7.2)	32	(6.4)
Severe	7	(1.4)	10	(2.0)
Unknown Severity	28	(5.8)	22	(4.4)

*Includes patients with severe AE's and AE's of unknown severity. Review of patients with AE's of unknown severity did not reveal anything to suggest that the two treatment arms were different.

Comparison With Clarithromycin

Adverse experience data are summarized for — Study 548 which compared 7 day treatment with Augmentin XR to 7 day treatment with clarithromycin 500mg b.i.d.. Study 548 was the only study in this NDA which used clarithromycin as the comparator.

Most Frequent Adverse Experiences by Preferred Term in Controlled Clinical Study 548

During the interval on-therapy plus 30 days post-therapy, at least one AE was reported by approximately 65% of patients in both the Augmentin XR and clarithromycin groups. The most frequently occurring AE was diarrhea, which was reported by 27.6% of patients in the Augmentin XR group and 11.5% of patients in the clarithromycin group (P<0.01). The proportion of patients developing headache (7.2% and 5.1%, respectively; P=0.31) and nausea (6.6% and 6.8%, respectively; P=0.87) was similar between the Augmentin XR and clarithromycin group. The proportion of patients reporting abdominal pain in the Augmentin XR group was 3.1% compared to 5.8% in the clarithromycin group (P=0.16). The proportion of patients experiencing genital moniliasis in the Augmentin XR group was 5.5% compared to 0.7% in the clarithromycin group (P<0.01). The proportion of patients experiencing taste perversion was only 1.0% in the Augmentin XR group compared with 11.5% of patients in the clarithromycin group (P<0.01).

Number (%) of Patients With the Most Frequently Occurring (≥2% in Either Treatment Group) Adverse Experiences by Preferred Term in Controlled Clinical Study 548 (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR		Clarithromycin 500mg	
	N=290		N=295	
Preferred Term	n	(%)	n	(%)
Patients with at Least One AE	191	(65.9)	193	(65.4)
Diarrhea	80	(27.6)	34	(11.5)
Headache	21	(7.2)	15	(5.1)
Nausea	19	(6.6)	20	(6.8)
Moniliasis Genital (Candidiasis)*	16	(5.5)	2	(0.7)
Infection Viral	12	(4.1)	5	(1.7)
Upper Respiratory Tract Infection	11	(3.8)	3	(1.0)
Rhinitis	10	(3.4)	14	(4.7)
Abdominal Pain	9	(3.1)	17	(5.8)
Injury	9	(3.1)	7	(2.4)
Infection Fungal	9	(3.1)	1	(0.3)
Vomiting	8	(2.8)	8	(2.7)
Sinusitis	7	(2.4)	12	(4.1)
Chest Pain	6	(2.1)	2	(0.7)
Pharyngitis	5	(1.7)	10	(3.4)
Constipation	5	(1.7)	7	(2.4)
Myalgia	5	(1.7)	7	(2.4)
Insomnia	4	(1.4)	7	(2.4)
Mouth Dry	4	(1.4)	7	(2.4)
Taste Perversion	3	(1.0)	34	(11.5)
Flatulence	3	(1.0)	11	(3.7)
Dizziness	3	(1.0)	6	(2.0)

* The percentage rate listed in this table is based on the total male + female population. In study 548, females made up approximately 55.8% of the total population. Therefore, if the rate were to be calculated based on total female population, then it would be approximately slightly less than double what is listed in this table.

A higher overall frequency of AEs was reported in Study 548 as compared to the combined controlled studies (approximately 63% vs. 50%, respectively) as well as for the five most frequently reported AEs in the Augmentin XR group: diarrhea (26.5% and 20.0%, respectively), nausea (6.1% and 4.7%, respectively), headache (6.7% and 3.5%, respectively) genital moniliasis (5.1% and 2.4%, respectively), and viral infection (3.8% and 1.6%, respectively).

Adverse Experiences by Relationship to Study Medication in Controlled Clinical Study 548

During the interval on-therapy and within 30 days post-therapy, 41.0% of patients in the Augmentin XR group and 32.9% of patients in the clarithromycin group reported at least one AE which the investigator considered to be of suspected or probable relationship to study medication. A greater proportion of patients in the Augmentin XR group (24.8%) reported episodes of diarrhea that were considered to be of suspected or probable relationship to study medication compared to the proportion of patients in the clarithromycin group (10.2%). In addition, 5.2% of Augmentin XR-treated patients developed genital moniliasis considered to be of suspected or probable relationship to study medication compared to 0.7% of clarithromycin-treated patients.

A greater proportion of patients in the clarithromycin group (10.8%) reported taste perversion that was considered to be of suspected or probable relationship to study medication compared to 1.0% of patients in the Augmentin XR group. The proportion of patients reporting abdominal pain of suspected or probable relationship to study medication was greater in the clarithromycin group than in the Augmentin XR group (4.4% and 1.7%, respectively).

Number (%) of Patients With the Most Frequently Occurring (≥1%) Adverse Experiences of Suspected/Probable Relationship to Study Medication in Controlled Clinical Study 548 (in Either Treatment Group On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=290		Clarithromycin 500mg N=295	
Preferred Term	n	(%)	n	(%)
Patients with at Least One AE of Suspected or Probable Relationship	119	(41.0)	97	(32.9)
Diarrhea	72	(24.8)	30	(10.2)
Moniliasis Genital (Candidiasis)*	15	(5.2)	2	(0.7)
Nausea	13	(4.5)	17	(5.8)
Infection Fungal	9	(3.1)	1	(0.3)
Abdominal Pain	5	(1.7)	13	(4.4)
Gastrointestinal Disorder NOS	4	(1.4)	1	(0.3)
Moniliasis	4	(1.4)	1	(0.3)
Taste Perversion	3	(1.0)	32	(10.8)
Flatulence	3	(1.0)	9	(3.1)
Vomiting	3	(1.0)	4	(1.4)
Headache	3	(1.0)	1	(0.3)
Mouth Dry	3	(1.0)	1	(0.3)
Pruritis Genital	2	(0.7)	3	(1.0)
Dyspepsia	0		5	(1.7)
Rash Erthyematous	0		3	(1.0)

NOS=not otherwise specified

* The percentage rate listed in this table is based on the total male + female population. In study 548, females made up approximately 55.8% of the total population. Therefore, if the rate were to be calculated based on total female population, then it would be approximately slightly less than double what is listed in this table.

Adverse Experiences by Severity in Controlled Clinical Study 548

Most AEs were of mild or moderate severity. The proportion of patients reporting severe AEs was 7.9% in the Augmentin XR group and 14.6% in the clarithromycin group. Of the 83 patients in the Augmentin XR group who reported diarrhea, only eight patients reported severe diarrhea (2.6% of patients overall; 9.6% of patients with diarrhea). Severe diarrhea was reported by a smaller proportion of patients in the clarithromycin group (0.9% of patients overall; 8.8% of patients with diarrhea).

Of 16 patients in the Augmentin XR group who reported genital moniliasis, one patient reported severe genital moniliasis (0.3% of patients overall; 6.3% of patients with genital moniliasis). In contrast, no patient in the clarithromycin group reported a severe AE of genital moniliasis.

Of the 17 patients in the clarithromycin group who reported abdominal pain, three patients reported severe abdominal pain (0.9% of patients overall; 17.6% of patients with abdominal pain). In contrast, of the 9 patients in the Augmentin XR group who reported abdominal pain, only one patient reported severe abdominal pain (0.3% of patients overall; 11.1% of patients with abdominal pain).

Of 34 patients in the clarithromycin group who reported taste perversion, only 4 patients reported severe taste perversion (1.3% of patients overall; 11.8% of patients with taste perversion). There were no reports of severe taste perversion in the Augmentin XR group.

Number (%) of Patients with at Least One Adverse Experience, by Severity in Controlled Clinical Study 548 (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=290		Clarithromycin N=295	
Severity of Adverse Experience	n	(%)	n	(%)
Mild	138	(47.6)	130	(44.1)
Moderate	97	(33.4)	100	(33.9)
Severe	23	(7.9)	43	(14.6)

Note:Patients who experienced a given AE more than once and at the same severity each time were counted only once for that AE.

Adverse Events Requiring Corrective Therapy

Diarrhea

Augmentin XR had increased rates of adverse events requiring corrective therapy with regards to two specific adverse events: diarrhea and genital moniliasis. The tables below summarize the rates of these adverse events for diarrhea.

Number of Patients (%) with Diarrhea Requiring Corrective Therapy for Controlled Trials in NDA 50-785: Augmentin XR (16:1) vs. Comparators

	Diarrhea Requiring Corrective Therapy					
	Augmentin XR			Comparator		
	n (number of patients)	(%) (Percent of total in study arm)	N (total number in study arm)	n (number of patients)	(%) (Percent of total in study arm)	N (total number in study arm)
Study 546 (Augmentin 7:1)	10	(3.9)	255	5	(1.9)	259
Study 548 (Clarithromycin)	20	(6.4)	313	4	(1.3)	318
Study 549 (Levofloxacin)	14	(4.2)	331	3	(0.9)	340
Study 550 (Levofloxacin)	9	(4.2)	212	4	(1.9)	216
Study 556* (Augmetin 1gr)	13	(7.7)	169	14	(8.0)	175
Total	66	(5.9)	1111	30	(2.6)	1133

- This formulation of Augmentin is approved for use in Europe (not in U.S.) and is given in doses of 1000mg amox/125mg clavulanate po TID. The total daily dose of amoxicillin is 3,000 mg per day while the total dose of amoxicillin for the US approved Augmentin formulation (used in Study 546) was 1,750 mg per day. The European formulation also contains 125 mg more of clavulanate per day..

The study drug did have higher rates of diarrhea requiring corrective therapy than all comparators except for the European formulation of Augmentin, Augmentin 1gr. This may be the result of a higher daily amount of clavulanate contained in Augmentin 1 gr (375mg clavulanate for Augmentin 1 gr vs. 250mg clavulanate for Augmentin XR). In the label for Augmentin 875, it noted that in the supporting studies, the rates of severe diarrhea/diarrhea requiring withdrawal were higher in the arm which contained more clavulanate (2.5% for Augmentin 500mg amox/125mg clavulanate TID vs. 1.0% for Augmentin 875mg amox/125 mg clavulanate B.I.D.). This suggests that the daily amount of clavulanate may be responsible for increased rates of diarrhea requiring corrective therapy in the active control arm of study 556, despite the fact that the active control arm had a lower overall rate of diarrhea (9.7% vs. 14.3%). In the comparison of Augmentin 875mg amoxicillin vs. Augmentin XR, the amounts of daily clavulanate are the same but the daily amoxicillin content of Augmentin XR is much higher (4,000mg vs. 1,750 mg). This suggests that both the daily amoxicillin content and the daily clavulanate content may contribute to the rates of diarrhea requiring corrective therapy.

Types of Corrective Therapy for Diarrhea

The majority of corrective therapy which was administered for the treatment of diarrhea in this NDAinvolved treatment with anti-diarrheal medication as is displayed by the tables below. There were very few cases of diarrhea in any treatment arm which required more aggressive therapy with antibiotics, IV fluids, or an advanced procedure such as colonoscopy.

Types of Corrective Therapy for Diarrhea in Controlled and Uncontrolled Clinical Trials

	Treatment with Anti-Diarrheal		Treatment with Flagyl		I..V. Fluids		Colonoscopy or Advanced Radiological Procedure	
	Treatment Arm		Treatment Arm		Treatment Arm		Treatment Arm	
Study (control drug)	AugXR	Control	AugXR	Control	AugXR	Control	AugXR	Control
546 (Augmentin 875)	9	5	1	0	0	0	0	0
547 (no control)	12	No control	0	No control	2	No control	1	No control
548 (clarithromycin)	18	0	0	1	0	0	0	0
550 (levofloxacin)	9	4	1	0	0	0	1	0
551 (no control)	25	No control	0	No control	0	No control	0	No control
556 (Augmentin 1gr*	13	14	0	0	0	0	0	
Total	86	23	2	1	2	0	2	0

* This formulation of Augmentin is approved for use in Europe and is given in doses of 1000mg amox/125mg clavulanate po TID. The total daily dose of amoxicillin is 3,000 mg per day while the total dose of amoxicillin for the US approved Augmentin formulation (used in Study 546) was 1,750 mg per day. The European formulation also contains 125 mg more of clavulanate per day.

Genital Moniliasis

For genital moniliasis, there was a low but increased rate of patients who required corrective therapy in the study drug arm as is shown in the table below.

Percentages of Patients Requiring Corrective Therapy for Genital Moniliasis in All Exposed Population			
AE requiring Corrective therapy	**Augmentin XR (all patients in NDA)**	**All Comparators**	**Augmentin 875 (Study 546)**
Genital Moniliasis*	1.8%	0.5%	0.9%

* This percentage rate was calculated based on total male + female population. In the all exposed category, females made up 50.7% of the total patient population. Therefore, the percentage rate listed in the table above would be approximately half of what would be calculated if it were based on the female population only.

Discussion of Adverse Events

For the Augmentin XR Phase III studies, diarrhea was the most frequently reported AE in the combined controlled and uncontrolled studies, occurring in 18.7% of patients treated with Augmentin XR. 4.2% of patients with diarrhea required corrective treatment. No relationship was identified between the occurrence of diarrhea in the Augmentin XR studies and the variables of gender and age. The higher incidence of diarrhea in the Phase III studies as contrasted to the Clinical Pharmacology Studies (3.7%) is a reflection of the fact that subjects only received single doses of Augmentin XR. Nausea, vomiting, abdominal pain, headache, genital moniliasis and vaginitis were reported by ≤5% of patients who received Augmentin XR and were mild to moderate in severity for the majority of occurrences.

In the Augmentin XR Phase III clinical program, the frequency of diarrhea ranged from 17.4% in the uncontrolled studies to 26.5% in the — controlled study with clarithromycin as the comparator.

The diarrhea rate for Augmentin XR was not significantly different from the rate for the Augmentin 1000/125mg tid comparator in Study 556. Interestingly, Study 556, which was conducted in Europe, reported the lowest diarrhea rate for Augmentin XR (13.0%) and an Augmentin comparator (9.7%) of all the studies in the Augmentin XR Phase III program.

Superinfections with mycotic pathogens including genital moniliasis (candidiasis), moniliasis and fungal infection (WHO-ART resistance mechanisms) were reported by a small proportion of patients in the controlled Augmentin XR clinical studies. Almost all of these AEs were considered to be related to study medication and the majority of AEs were mild to moderate in severity with a nonserious outcome resolving with treatment. It is not clear if the occurrence of these superinfections is dose-related because of the similar incidence in the comparison of Augmentin XR to Augmentin 875/125mg b.i.d. in Study 546.

For the Augmentin XR group (combined controlled analysis during the on-therapy and within 30 days interval) the AEs that pertained to the liver were nonserious and included, by preferred term, increased SGOT (0.5%, 6 patients), increased SGPT (0.7%, 9 patients, 4 of which are also included with increased SGOT), hepatic enzymes increased (0.4%, 5 patients), bilirubinemia (0.2%, 2 patients), and hepatic function abnormal (0.2%, 3 patients; included verbatim term of increased liver function tests). Most of these AEs (laboratory abnormalities) resolved without corrective treatment and did not require withdrawal from the study. There was no evidence of liver failure/hepatic dysfunction as a consequence of these laboratory elevations. There was one report of hepatocellular damage in a patient taking Augmentin XR which was considered to be unrelated to study medication.

The clinical studies demonstrate that Augmentin XR was generally well-tolerated in controlled and uncontrolled clinical studies with a favorable adverse experience profile. The AE profile of Augmentin XR was similar to that of the established AE profile for Augmentin 875/125mg b.i.d., including gastrointestinal AEs, the body system with the most frequently reported AEs in either treatment group. However, there did appear to be a higher incidence of diarrhea and genital moniliasis in the Augmentin XR arm as well as a higher incidence of these adverse events which required corrective therapy. Primarily, these advserse events were not

serious and the type of corrective therapy was not extensive. There were few severe AEs and few AEs occurring after the completion of therapy.

Conclusions of Adverse Events Data

- Augmentin XR was generally well-tolerated in the three completed Clinical Pharmacology studies.

- Augmentin XR was generally well-tolerated in controlled and uncontrolled 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 b.i.d. in a direct comparison of the two treatments, including gastrointestinal AEs, the body system with the most frequently reported AEs in either treatment group. The profile for Augmentin XR did not differ markedly from the established AE profile for Augmentin 875/125mg b.i.d., except for an increased rate of diarrhea which did not reach statistical signficance (18.0% vs 14.3%). Diarrhea requiring corrective therapy occurred in 10 patients in the Augmentin XR arm as compared to 5 patients in the Augmentin 875 arm.

- Diarrhea (18.7%) was the only AE reported by ≥5% of Augmentin XR-treated patients overall in the Phase III 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, however, the Augmentin XR group did have a higher rate of diarrhea and genital moniliasis.

- 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.

- There was an increased rate of diarrhea and genital moniliasis for the Augmentin XR arm which requiried corrective therapy. The type of corrective therapy typically involved the use of anti-diarrheal medicaitons and anti-fungal medicaitons. There were only rare instances where more significant or invasive therapy was necessary.

Deaths

No deaths were reported in any of the subjects in the three Clinical Pharmacology studies either during the studies or up to 30 days after the last dose of study medication.

Fifteen patients in the seven studies of the Augmentin XR Phase III clinical program had serious adverse experiences (SAEs) associated with death with SAE onsets in the interval from first dose to within 30 days of last dose. All of the deaths occurred in CAP studies. Serious AEs associated with death were reported in 14/2559 patients who received Augmentin XR and in 1/1308 patients who received a comparator medication (Augmentin 875/125mg in Study 546). Of the 14 Augmentin XR-treated patients having SAEs associated with death, five were enrolled in the controlled CAP studies (3 patients in Study 546, 2 patients in Study 556, with 424 patients in total receiving Augmentin XR) and nine participated in uncontrolled CAP Study 547 (420 patients receiving Augmentin XR).

Cardiac failure (3 patients) was the most frequently reported SAE associated with death for patients who received Augmentin XR. All other SAEs associated with death were reported by ≤ 2 patients and most were categorized in the cardiovascular and vascular (extracardiac) body systems. All SAEs associated with death

were considered by the investigator to be due to the condition under study or to pre-existing medical conditions, and either unrelated or unlikely to be related to study medication.

Two patients died > 30 days post-therapy although the SAEs associated with death began within 30 days post-therapy. The SAEs associated with death were pulmonary carcinoma (Study 546) and neoplasm (Study 547). In addition to these 2 deaths, there were three further deaths which occurred >30 days after the cessation of study medication and were reported only to the SB safety database —— The SAEs associated with death were: aggravation of pneumonia (controlled CAP Study 556), pulmonary carcinoma —— controlled Study 549) and respiratory insufficiency/pulmonary edema —— controlled Study 549). The aggravation of pneumonia had an onset on-therapy; the other SAEs started within 30 days post-therapy. These three patients received Augmentin XR during the double-blind treatment period.

All SAEs associated with death in any time interval were considered by the investigators to be either unrelated or unlikely to be related to treatment with Augmentin XR or comparators.

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

Onset of SAE:	**On Therapy**		**Within 30 days Post Therapy**	
	Augmentin XR N= 2423	**All Comparators N= 1226**	**Augmentin XR N= 2423**	**All Comparators N= 1226**
Patients with at least one SAE associated with death	3 (0.1)	0	11* (0.5)	1 (0.08)
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n(%)**
Cardiac Failure	0	0	3 (0.12)	0
Embolism Pulmonary	0	0	2 (0.08)	0
Neoplasm (NOS)	0	0	2* (0.08)	0
Cardiac Arrest	0	0	1 (0.04)	1 (0.08)
Cardiac Failure (left)	0	0	1 (0.04)	0
Cardiomyopathy	0	0	1 (0.04)	0
Cerebrovascular Accident	1 (0.04)	0	0	0
Myocardial Infarction	1 (0.04)	0	1 (0.04)	0
Pneumonia	0	0	1 (0.04)	0
Pulmonary Carcinoma	0	0	1* (0.04)	0
Respiratory insufficiency	0	0	1 (0.04)	0
Respiratory Disorder	1 (0.04)	0	0	0

*Patient 547.191.06385 with neoplasm (NOS) and Patient 546.104.13872 with pulmonary carcinoma died >30 days post-therapy although SAE onset was within 30 days post-therapy.

Although there are substantially more deaths amongst patients who received treatment with Augmentin XR, all deaths were determined by the investigators to be "unlikely" to be related or "unrelated" to the study medications. The one patient who died of "respiratory insufficiency" 2 days after completion of 4 days of therapy with Augmentin XR, was a 71 year old man who had a history of atrial fibrillation and hypoproteinemia. No autopsy was done and the investigator reported "lung congestion" as the cause of death. This was felt to be unrelated to study medication.

Serious Adverse Experiences

None of the 59 subjects who participated in the three clinical pharmacology studies with Augmentin XR had serious AEs.

In the five completed controlled studies of the phase III clinical program, the proportions of patients reporting serious AEs during the on-therapy and within 30 days post-therapy interval were similar and relatively low in both treatment groups: Augmentin XR: 3.6%; All Comparators: 4.4%. Most of these patients had serious AEs which were considered to be unrelated or of unlikely relationship to study medication.

Number (%) of Patients (≥2 Patients in Either Group) With Serious Adverse Experiences in Controlled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226	
Preferred Term	n	(%)	n	(%)
Patients with at Least One Serious AE	43	(3.6)	54	(4.4)
Pneumonia	8	(0.7)	9	(0.7)
Respiratory Disorder	4	(0.3)	1	(0.1)
Neoplasm NOS*	3	(0.3)	2	(0.2)
Cardiac Failure	2	(0.2)	5	(0.4)
Chronic Obstructive Airways Disease	2	(0.2)	3	(0.2)
Pulmonary Carcinoma	2	(0.2)	3	(0.2)
Dyspnea	2	(0.2)	1	(0.1)
Respiratory Insufficiency	2	(0.2)	1	(0.1)
Diarrhea	2	(0.2)	0	
Therapeutic Response Increased	1	(0.1)	4	(0.3)
Asthma	1	(0.1)	3	(0.2)
Bronchitis	1	(0.1)	2	(0.2)
Injury	1	(0.1)	2	(0.2)
Abscess	0		2	(0.2)
Cellulitis	0		2	(0.2)
GI Hemorrhage	0		2	(0.2)
Pleural Effusion	0		2	(0.2)

* NOS= not otherwise specified

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Number (%) of Patients With Serious Adverse Experiences of Suspected or Probable Relationship to Study Medication in Controlled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226	
Preferred Term	n	(%)	n	(%)
Patients with at Least One Serious AE of Suspected or Probable Relationship to Study Medication	4	(0.3)	5	(0.4)
Diarrhea	2	(0.2)	0	
Abdominal Pain	1	(0.1)	0	
Colitis	1	(0.1)	0	
Pneumonia	1	(0.1)	2	(0.2)
Gastritis	0		1	(0.1)
Respiratory Disorder	0		1	(0.1)
Therapeutic Response Increased	0		1	(0.1)

Number (%) of Patients (≥2 Patients) with Serious Adverse Experiences in Uncontrolled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Treatment Group	
	Augmentin XR N=1224	
Preferred Term	n	(%)
Patients with at Least One Serious AE	25	(2.0)
Pneumonia	7	(0.6)
Cardiac Failure	4	(0.3)
Embolism Pulmonary	2	(0.2)
Pulmonary Carcinoma	2	(0.2)

In the two uncontrolled clinical studies, 2.0% of patients who received Augmentin XR reported serious AEs during the interval on-therapy and within 30 days post-therapy. Serious AEs of suspected or probable relationship to study medication were reported by two patients.

During the on-therapy and within 30 days post-therapy interval, similar proportions of patients in both treatment groups of controlled clinical CAP Study 546 reported serious AEs: Augmentin XR: 5.9%; Augmentin 875/125mg b.i.d.: 7.3%. Of these patients, two in the Augmentin XR group and one in the Augmentin 875/125mg group experienced serious AEs which were considered by the investigator to be of suspected or probable relationship to study medication.

The incidence of serious AEs in studies comparing Augmentin XR with levofloxacin and clarithromycin was low with no individual-preferred term serious AE reported by more than two patients.

Withdrawals Due to Adverse Experiences

In the three completed Clinical Pharmacology studies, 5 (8.5%) patients were withdrawn due to AEs. The most frequently reported AE leading to withdrawal was genital moniliasis (6.8%), all of which were considered to be probably related to the study medication.

In the five completed controlled studies of the phase III clinical program, the proportions of patients withdrawn due to AEs during the interval 'on-therapy and within 30 days post-therapy' were low and the incidence was similar between the treatment groups: Augmentin XR: 4.4%; All Comparators: 4.3%. The most frequently occurring AEs leading to withdrawal in the Augmentin XR group were diarrhea (1.0%), pneumonia and nausea (each 0.5%). In the All Comparators group, the most frequently occurring AEs leading to withdrawal were pneumonia (0.6%), diarrhea and nausea (each 0.4%).

Number (%) of Patients ≥2 Patients in Either Treatment Group Withdrawn Due to Adverse Experiences in Controlled Clinical Studies (On-Therapy and Within 30 Days Post Therapy)

	Treatment Group			
	Augmentin XR N = 1199		All Comparators N = 1226	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients With at Least One AE Leading to Withdrawal	53	(4.4)	53	(4.3)
Diarrhea	12	(1.0)	5	(0.4)
Pneumonia	6	(0.5)	7	(0.6)
Nausea	6	(0.5)	5	(0.4)
Abdominal Pain	3	(0.3)	2	(0.2)
Vomiting	3	(0.3)	2	(0.2)
Dizziness	2	(0.2)	3	(0.2)
Urticaria	2	(0.2)	2	(0.2)
Headache	2	(0.2)	1	(0.1)
Respiratory Disorder	2	(0.2)	1	(0.1)
Respiratory Insufficiency	2	(0.2)	1	(0.1)
Cardiac Failure	1	(0.1)	2	(0.2)
COPD	0		2	(0.2)
Dyspepsia	0		2	(0.2)
Gastritis	0		2	(0.2)
Accidental Overdose	0		2	(0.2)

In the two uncontrolled clinical studies, 2.7% of patients reported AEs leading to withdrawal during the interval 'on-therapy and within 30 days post-therapy'. The most frequently occurring AE leading to withdrawal was diarrhea (1.0%).

Number (%) of Patients (≥2 Patients) Withdrawn Due to Adverse Experiences in Uncontrolled Clinical Studies (On-Therapy and Within 30 Days Post-Therapy)

	Augmentin XR N = 1224	
Preferred Term	**n**	**(%)**
Patients With at Least One AE Leading to Withdrawal	33	(2.7)
Diarrhea	12	(1.0)
Pneumonia	5	(0.4)
Abdominal Pain	3	(0.2)
Nausea	3	(0.2)
Cardiac Failure	2	(0.2)
Fever	2	(0.2)
Headache	2	(0.2)
Vomiting	2	(0.2)

In controlled clinical CAP Study 546 which compared Augmentin XR with conventional Augmentin 875/125mg b.i.d., 3.5% of Augmentin XR-treated patients and 6.9% of Augmentin 875/125mg-treated patients experienced AEs leading to withdrawal during the interval 'on-therapy and within 30 days post-therapy'. Worsening of pneumonia was the most frequently occurring AE leading to withdrawal in both treatment groups (Augmentin XR: 0.8%; Augmentin 875/125mg: 1.5%). In this study only one patient (0.4%) in the Augmentin XR arm and two patients (0.8%) in the comparator arm, Augmentin 875, withdrew because of diarrhea.

Pregnancies

No pregnancies occurred during the clinical pharmacology studies. In the Phase III clinical program, two pregnancies (one in the Augmentin XR group, one in the levofloxacin group) were reported either on therapy or within 30 days of the last dose of study medication. Exposure to study medication occurred during the first trimester in both cases. Each woman delivered a healthy baby girl.

Clinical Laboratory Evaluations

A review of the clinical laboratory data from 59 subjects who received Augmentin XR either alone or in combination with Maalox in three Phase I studies shows that there was a very low frequency of treatment-emergent changes. There were no consistent or clinically significant effects on any clinical chemistry, hematology or urinalysis parameter for any subject who received Augmentin XR. No observed change was considered by the investigator to be of clinical significance.

In the Phase III controlled clinical studies, the proportion of patients with F2F3-flagged values (laboratory values which had changed from baseline by more than the pre-specified amount and were also outside the pre-specified extended normal range) at end of therapy for any specific hematology parameter (with the exception of platelets) in either treatment group was ≤0.5%.

MO COMMENT: *The medical officer accepts the applicant's criteria used for flagging abnormal results.*

The proportion of patients in either treatment group with F2F3-flagged elevated platelets was ≤3.5%. In the Augmentin XR group, seventy percent of those patients flagged for elevated platelets were CAP patients. In the controlled clinical studies, investigators reported four patients with an adverse experiences (AE) of thrombocythemia (two patients in the Augmentin XR group and two patients in the all comparators group), and one of these patients (in the Augmentin XR group) had an F2F3-flagged elevated platelet value. In addition, in the controlled studies, the proportion of patients with F2F3-flagged values for any specific liver function parameter was ≤1.6%. Further, the proportion of patients with F2F3-flagged values for any other metabolic function parameter was also low (≤1.0%). The proportion of patients in the controlled studies with an F3 transition from screening to the on-therapy visit for any specific urinalysis parameter (with the exception of WBCs) was ≤1.5%, in either treatment group. The proportion of patients with an F3 transition for WBCs in either treatment group was ≤3.1%.

Number (%) of Patients with Hematology Values of Potential Clinical Concern (F2F3-Flagged) at End of Therapy in Controlled Clinical Studies

Functional Group/ Parameter		Treatment Group			
		Augmentin XR		All Comparators	
Hematology	F2F3 Flag	n/N*	(%)	n/N	(%)
Hematocrit	High	0/1082		1/1124	(0.1)
	Low	1/1082	(0.1)	1/1124	(0.1)
Neutrophils Absolute	High	6/1072	(0.6)	3/1114	(0.3)
	Low	2/1072	(0.2)	5/1114	(0.4)
Platelets	High	40/1080	(3.7)	22/1123	(2.0)

	Low	2/1080	(0.2)	3/1123	(0.3)

* n/N=number of patients with flag/number of patients evaluated for the specific parameter.

Number (%) of Patients with Clinical Chemistry Values of Potential Clinical Concern (F2F3-Flagged) at End of Therapy in Controlled Clinical Studies

		Treatment Group			
Functional Group/Parameter		**Augmentin XR**		**All Comparators**	
Clinical Chemistry	**F2F3 Flag**	**n/N***	**(%)**	**n/N**	**(%)**
Liver Function					
ALT	High	15/1099	(1.4)	15/1154	(1.3)
AST	High	5/1098	(0.5)	6/1153	(0.5)
Alkaline Phosphatase	High	4/1097	(0.4)	6/1155	(0.5)
Total Bilirubin	High	1/1097	(0.1)	2/1156	(0.2)
Renal Function and Serum Electrolytes					
Serum Creatinine	High	2/1097	(0.2)	0/1158	
Blood Urea Nitrogen	High	1/1106	(0.1)	0/1159	
Calcium	High	1/1100	(0.1)	0/1155	
	Low	2/1100	(0.2)	1/1155	(0.1)
Potassium	High	5/1099	(0.5)	2/1154	(0.2)
Sodium	High	1/1109	(0.1)	0/1160	
	Low	0/1109		1/1160	(0.1)
Total Protein	Low	1/1106	(0.1)	0/1159	
Other Metabolic Functions					
Creatine Kinase**	High	5/822	(0.6)	4/864	(0.5)

* n/N=number of patients with flag/number of patients evaluated for the particular parameter.

** In Study 549, F2F3-flagging criteria for creatine kinase were not correctly applied. Hence, patients from Study 549 are not included under "Creatine Kinase". However, patient 549.195.04508 (levofloxacin) had an F2F3-flagged elevated creatine kinase value at end of therapy.

Number (%) of Patients with F3 Transitions in Urinalysis Values From the Screening to On-Therapy Visits in Controlled Clinical Studies

	F3 Transition to High			
Urinalysis Parameter	**Augmentin XR**		**All Comparators**	
	n/N*	**(%)**	**n/N**	**(%)**
Glucose	8/978	(0.8)	17/1025	(1.7)
Protein	3/994	(0.3)	1/1037	(0.1)
RBCs	16/1004	(1.6)	10/1067	(0.9)
WBCs	27/943	(2.9)	29/970	(3.0)

* n/N=number of patients with flag/number of patients evaluated for the particular parameter.

Note: WBCs=white blood cells; RBCs=red blood cells.

Both the frequency and pattern of all F2F3-flagged parameters (hematology, clinical chemistry, and urinalysis) at end of therapy for Augmentin XR-treated patients in the controlled studies matched well the results seen for Augmentin XR-treated patients in the uncontrolled studies and for all patients exposed to Augmentin XR.

Number (%) of Patients with Hematology and Clinical Chemistry Values of Potential Clinical Concern (F2F3-Flagged) at End of Therapy in Uncontrolled Clinical Studies

Functional Group/Parameter		Augmentin XR	
Hematology	**F2F3 Flag**	**n/N***	**(%)**
Hemoglobin	Low	1/1155	(0.1)
	High and Low	1/1155	(0.1)
Hematocrit	High	2/1155	(0.2)
	Low	1/1155	(0.1)
	High and Low	1/1155	(0.1)
RBCs	High	1/1154	(0.1)
	Low	1/1154	(0.1)
Neutrophils Absolute	High	8/1142	(0.7)
	Low	13/1142	(1.1)
Platelets	High	46/1152	(4.0)
	Low	1/1152	(0.1)
Liver Function			
ALT	High	23/1167	(2.0)
AST	High	13/1160	(1.1)
Alkaline Phosphatase	High	3/1166	(0.3)
Total Bilirubin	High	1/1167	(0.1)
Renal Function and Serum Electrolytes			
Serum Creatinine	High	1/1169	(0.1)
Blood Urea Nitrogen	High	1/1172	(0.1)
Calcium	High	3/1166	(0.3)
	Low	4/1166	(0.3)
	High and Low	1/1166	(0.1)
Potassium	High	1/1163	(0.1)
	Low	1/1163	(0.1)
Sodium	Low	1/1174	(0.1)
Total Protein	Low	1/1171	(0.1)
Albumin	Low	4/1171	(0.3)
Other Metabolic Functions			
Creatine Kinase	High	10/1134	(0.9)

* n/N=number of patients with flag/number of patients evaluated for the particular parameter.

Number (%) of Patients with F3 Transitions in Urinalysis Values From the Screening to On-Therapy Visits in Uncontrolled Clinical Studies

	F3 Transition Within_High	
Urinalysis Parameter	**Augmentin XR n/N***	**(%)**
Glucose	5/1098	(0.5)
Protein	10/1071	(0.9)
RBCs	25/1087	(2.3)
WBCs	29/953	(3.0)

* n/N=number of patients with flag/number of patients evaluated for the particular parameter.
Note: WBCs = white blood cells; RBCs = red blood cells.

In CAP Study 546, the frequency and pattern of all F2F3-flagged parameters at end of therapy in Augmentin XR-treated patients matched well those seen in patients treated with Augmentin 875/125mg. Lastly, the frequency and pattern of all F2F3-flagged parameters in patients who received Augmentin XR were similar to those seen in patients treated with either levofloxacin or clarithromycin.

Drug-Drug Interactions

Clinical Pharmacology Study 583 was an open-label, randomized, formal drug interaction study to investigate the effect of Maalox® Antacid on the bioavailability of Augmentin XR. The study enrolled 20 subjects and was conducted using a crossover design. The frequency of AEs was similar to that of subjects who received Augmentin XR alone. The analyses of AE data showed that concomitant administration of Augmentin XR with Maalox® antacid simultaneously and two hours apart, did not affect the tolerability profile of Augmentin XR.

In the Phase III controlled clinical studies, eight concomitant drugs and/or drug classes (i.e., paracetamol, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, pseudoephedrine HCl, theophylline or aminophylline, oral contraceptives, allopurinol, and drugs with the potential to increase gastric pH) were analyzed for a potential clinical drug-drug interaction with Augmentin XR. For two of the eight patient cohorts (oral contraceptives and allopurinol), the size was too small to draw clear conclusions about potential drug interactions.

Number (%) of Patients in Controlled Studies Who Received Selected Concomitant Medications

	Cohort Size			
	Augmentin XR N=1199		All Comparators N=1266	
Reason for Inclusion in Drug-Drug Analysis	n	(%)	n	(%)
Concomitant Drug (and/or Drug Class)				
Frequency of Use				
Paracetamol	339	(28.3)	370	(29.2)
Non-Steroidal Anti-Inflammatory Agents	218	(18.2)	197	(15.6)
Acetylsalicylic Acid	146	(12.2)	168	(13.3)
Pseudoephedrine HCl	118	(9.8)	114	(9.0)
Influence on Absorption				
Drugs Which have the Potential To Increase Gastric pH	210	(17.5)	211	(16.7)
Narrow Therapeutic Index				
Theophylline or Aminophylline	102	(8.5)	110	(8.7)
Known Interactions with Other Antibiotics				
Oral Contraceptives	43	(3.6)	50	(4.0)
Allopurinol	20	(1.7)	18	(1.4)

The Five Most Frequently Occurring Adverse Experiences (by Descending Order) in Controlled Clinical Studies as Contrasted With the Frequency of These AEs in Patients Taking Select Concomitant Medications

	All Controlled Studies				Paracetamol				NSAIDs				Potential to Increase Gastric pH			
	Treatment Group				Treatment Group				Treatment Group				Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226		Augmentin XR N=339		All Comparators N=370		Augmentin XR N=218		All Comparators N=197		Augmentin XR N=210		All Comparators N=211	
Preferred Term	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with at least one AE	612	(51.0)	618	(50.4)	170	(50.1)	179	(48.4)	106	(48.6)	99	(50.3)	116	(55.2)	110	(52.1)
Diarrhea	240	(20.0)	114	(9.3)	84	(24.8)	41	(11.1)	54	(24.8)	19	(9.6)	60	(28.6)	24	(11.4)
Nausea	58	(4.8)	69	(5.6)	16	(4.7)	26	(7.0)	9	(4.1)	17	(8.6)	13	(6.2)	17	(8.1)
Headache	45	(3.8)	42	(3.4)	19	(5.6)	15	(4.1)	6	(2.8)	14	(7.1)	8	(3.8)	8	(3.8)
Abdominal Pain	29	(2.4)	40	(3.3)	5	(1.5)	12	(3.2)	3	(1.4)	8	(4.1)	4	(1.9)	12	(5.7)
Moniliasis Genital	31	(2.6)	8	(0.7)	6	(1.8)	0		4	(1.8)	2	(1.0)	3	(1.4)	1	(0.5)

	All Controlled Studies				Acetylsalicylic Acid				Pseudoephedrine HCl				Theophylline or Aminophylline			
	Treatment Group				Treatment Group				Treatment Group				Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226		Augmentin XR N=146		All Comparators N=168		Augmentin XR N=118		All Comparators N=114		Augmentin XR N=102		All Comparators N=110	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with at least one AE	612	(51.0)	618	(50.4)	65	(44.5)	87	(51.8)	66	(55.9)	47	(41.2)	25	(24.5)	32	(29.1)
Diarrhea	240	(20.0)	114	(9.3)	27	(18.5)	21	(12.5)	33	(28.0)	9	(7.9)	5	(4.9)	5	(4.5)
Nausea	58	(4.8)	69	(5.6)	13	(8.9)	9	(5.4)	9	(7.6)	8	(7.0)	1	(1.0)	2	(1.8)
Headache	45	(3.8)	42	(3.4)	11	(7.5)	10	(6.0)	6	(5.1)	2	(1.8)	2	(2.0)	2	(1.8)
Abdominal Pain	29	(2.4)	40	(3.3)	2	(1.4)	10	(6.0)	3	(2.5)	2	(1.8)	2	(2.0)	2	(1.8)
Moniliasis Genital	31	(2.6)	8	(0.7)	2	(1.4)	0		4	(3.4)	0		0		0	

(cont.) The Five Most Frequently Occurring Adverse Experiences (by Descending Order) as Contrasted with the Frequency of These AEs in Patients in Controlled Clinical Studies Taking Select Concomitant Medications

	All Controlled Studies Treatment Group				Oral Contraceptives Treatment Group				Allopurinol Treatment Group			
	Augmentin XR N=1199		All Comparators N=1226		Augmentin XR N=43		All Comparators N=50		Augmentin XR N=20		All Comparators N=18	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with at least one AE	612	(51.0)	618	(50.4)	20	(46.5)	16	(32.0)	8	(40.0)	4	(22.2)
Diarrhea	240	(20.0)	114	(9.3)	9	(20.9)	4	(8.0)	0		2	(11.1)
Nausea	58	(4.8)	69	(5.6)	4	(9.3)	3	(6.0)	1	(5.0)	0	
Headache	45	(3.8)	42	(3.4)	1	(2.3)	2	(4.0)	2	(10.0)	0	
Abdominal Pain	29	(2.4)	40	(3.3)	0		1	(2.0)	1	(5.0)	0	
Moniliasis Genital	31	(2.6)	8	(0.7)	4	(9.3)	0		0		0	

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The AE profile for patients taking the specified concomitant drugs (and/or drug classes) was similar to that observed in the Augmentin XR controlled studies. The most frequently reported AEs were diarrhea, nausea, and headache. However, the frequency of diarrhea varied, i.e., higher in patients taking a concomitant drug with the potential to increase gastric pH or concomitant pseudoephedrine hydrochloride and lower in patients taking concomitant theophylline/ aminophylline or allopurinol.

Although variable diarrhea frequencies were observed in a few cohorts, confounding factors, such as, the underlying medical history, baseline symptomatology, individual country variation both in the definition of diarrhea and AE reporting rates, and the administration of other concomitant medications with the side effect of diarrhea, may have contributed to this variability in diarrhea frequency.

In general, the AE profile observed in the specified concomitant drug (and/or drug class) cohorts, including those frequently administered to patients with CAP, sinusitis and —— was consistent with the AE profile of Augmentin XR demonstrated in the combined controlled studies.

Drug-Demographic Interactions

All Clinical Pharmacology studies were carried out in healthy subjects aged less than 60 years. In subjects who received Augmentin XR alone, the overall frequency of AE reporting per total subject sessions (108) was higher in female subjects (48.4%) than in male subjects (30.4%). In this treatment group headaches were the most frequently reported AE (per subject session) and occurred more frequently in females than males, 21.0% versus 10.9%. For female subjects genital moniliasis occurred in 9.7% of the total subject sessions.

In the Phase III clinical program, gender, age, race and country were examined in patients in the five completed double-blind, active-comparator clinical trials; in one completed uncontrolled study; and in an interim analysis from one ongoing, uncontrolled study in order to determine whether demographic factors affected the AE profile of Augmentin XR.

Drug-demographic effects were examined in both controlled studies and all exposed patients. The incidence of AEs in patients exposed to Augmentin XR was approximately 50% for each gender, age group (less than 65 years and at least 65 years old) and racial group (white, black, oriental and other). The proportion of all Augmentin XR-treated patients who reported at least one AE within the US was greater than that reported in patients outside the US, 56.8% versus 36.4%.

Overall there were no clinically appreciable differences in AEs reported by gender, age, racial origin or country. The incidence of diarrhea, however, varied by country among Augmentin XR-treated patients in the three countries that enrolled the most patients in the controlled studies (US 26.6%, France 17.7%, Germany 8.9%).

Number (%) of Patients with the Most Frequently Occurring (≥5%) Adverse Experiences

	Controlled Studies			
	Augmentin XR		All Comparators	
Preferred Term	Male N=596 n (%)	Female N=603 n (%)	Male N=612 n (%)	Female N=614 n (%)
Patients with at least one AE	283 (47.5)	329 (54.6)	289 (47.2)	329 (53.6)
Diarrhea	91 (15.3)	149 (24.7)	48 (7.8)	66 (10.7)
Nausea	25 (4.2)	33 (5.5)	24 (3.9)	45 (7.3)

	All-Exposed Patients			
	Overall		Augmentin XR By Gender	
Preferred Term	Augmentin XR N=2423 n (%)	All Comparators N=1226 n (%)	Male N=1179 n (%)	Female N=1244 n (%)
Patients with at least one AE	1162 (48.0)	618 (50.4)	531 (45.0)	631 (50.7)
Diarrhea	455 (18.8)	114 (9.3)	197 (16.7)	258 (20.7)
Nausea	99 (4.1)	69 (5.6)	40 (3.4)	59 (4.7)

Number (%) of Patients with the Most Frequently Occurring (≥5%) Adverse Experience

	Controlled Studies			
	Augmentin XR		All Comparators	
Preferred Term	< 65 years N=821 n (%)	_ 65 years N=378 n (%)	< 65 years N=866 n (%)	_ 65 years N=360 n (%)
Patients with at least one AE	432 (52.6)	180 (47.6)	444 (51.3)	174 (48.3)
Diarrhea	174 (21.2)	66 (17.5)	86 (9.9)	28 (7.8)
Nausea	41 (5.0)	17 (4.5)	56 (6.5)	13 (3.6)

	All Exposed Patients			
	Overall		Augmentin XR By Age	
Preferred Term	Augmentin XR N=2423 n (%)	All Comparators N=1226 n (%)	< 65 years N=1893 n (%)	_ 65 years N=530 n (%)
Patients with at least one AE	1162 (48.0)	618 (50.4)	900 (47.5)	262 (49.4)
Diarrhea	455 (18.8)	114 (9.3)	363 (19.2)	92 (17.4)
Nausea	99 (4.1)	69 (5.6)	76 (4.0)	23 (4.3)

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Number (%) of Patients with the Most Frequently Occurring (≥5% and in at least 5 patients) Adverse Experiences in either Treatment Group On-Therapy And Within 30 Days Post-Therapy by Race in Controlled Clinical Studies and All Exposed Patients

	Augmentin XR-Controlled Studies			
	White	Black	Oriental	Other*
	N=1085	N=58	N=8	N=48
Preferred Term	n (%)	n (%)	n (%)	n (%)
Patients with at least one AE	547 (50.4)	31 (53.4)	4 (50.0)	30 (62.5)
Diarrhea	210 (19.4)	14 (24.1)	3 (37.5)	13 (27.1)
Nausea	54 (5.0)	2 (3.4)	0	2 (4.2)
	All Comparators			
	White	Black	Oriental	Other*
	N=1119	N=56	N=7	N=44
Preferred Term	n (%)	n (%)	n (%)	n (%)
Patients with at least one AE	550 (49.2)	38 (67.9)	4 (57.1)	26 (59.1)
Diarrhea	98 (8.8)	9 (16.1)	2 (28.6)	5 (11.4)
Nausea	63 (5.6)	5 (8.9)	0	1 (2.3)
	Augmentin XR-All Exposed Patients			
	White	Black	Oriental	Other*
	N=2079	N=129	N=79	N=136
Preferred Term	n (%)	n (%)	n (%)	n (%)
Patients with at least one AE	984 (47.3)	65 (50.4)	40 (50.6)	73 (53.7)
Diarrhea	389 (18.7)	26 (20.2)	12 (15.2)	28 (20.6)
Nausea	82 (3.9)	7 (5.4)	5 (6.3)	5 (3.7)

*Includes Arab, Asian, Black Half-Breed, Cuban, Guyana-Indian, Half-Caste, Hispanic, Indian, Indian (Asian), Indian (India), Italian-American, Middle Eastern, Mixed, Native American, Native-American and German, North African, Pakistanian, Portuguese, Spanish and Undisclosed

Number (%) of Patients with the Most Frequently Occurring (≥5%) Adverse Experiences in either Treatment Group On-Therapy And Within 30 Days Post-Therapy in Controlled Clinical Studies and All Exposed Patients by Country (Countries with _100 Patients in Augmentin XR Group)

	Controlled Studies		All Exposed Patients
Preferred Term	Augmentin XR n (%)	All Comparators n (%)	Augmentin XR n (%)
United States	**N=622**	**N=642**	**N=1212**
Patients with at least one AE	389 (62.5)	401 (62.5)	721 (59.5)
Diarrhea	171 (27.5)	83 (12.9)	316 (26.1)
Nausea	45 (7.2)	51 (7.9)	70 (5.8)
Headache	36 (5.8)	31 (4.8)	66 (5.4)
France	**N=209**	**N=221**	**N=209**
Patients with at least one AE	101 (48.3)	109 (49.3)	101 (48.3)
Diarrhea	37 (17.7)	18 (8.1)	37 (17.7)
Nausea	2 (1.0)	10 (4.5)	2 (1.0)
Headache	4 (1.9)	3 (1.4)	4 (1.9)
Germany	**N=168**	**N=175**	**N=168**
Patients with at least one AE	46 (27.4)	36 (20.6)	46 (27.4)
Diarrhea	15 (8.9)	6 (3.4)	15 (8.9)
Nausea	4 (2.4)	0	4 (2.4)
Headache	3 (1.8)	4 (2.3)	3 (1.8)
Poland	**N=27**	**N=26**	**N=183**
Patients with at least one AE	10 (37.0)	15 (57.7)	47 (25.7)
Diarrhea	1 (3.7)	2 (7.7)	10 (5.5)
Nausea	0	1 (3.8)	6 (3.3)
Headache	1 (3.7)	1 (3.8)	3 (1.6)
Hungary*			**N=231**
Patients with at least one AE	–	–	56 (24.2)
Diarrhea	–	–	28 (12.1)
Nausea	–	–	2 (0.9)
Headache	–	–	3 (1.3)

* Hungary participated only in the uncontrolled studies; therefore, data are presented only for the All Exposed population.

Drug-Disease Interactions

Clinical pharmacology trials studies were conducted with healthy subjects therefore, drug-disease interactions were not assessed.

Across the — indications studied, during the interval on-therapy and within 30 days post-therapy, similar proportions of patients in the Augmentin XR treatment group reported at least one AE in combined controlled studies (for —— CAP) and in the individual controlled study (in ABS) (approximately 50%; range 48.8% for controlled CAP Studies to 54.7% for ABS Study 550). The proportions of patients who reported at least one AE in the two Augmentin XR uncontrolled studies were 56.4% (CAP Study 547) and 38.2% (ABS Study 551).

In combined —— Studies 548 and 549, the most frequently reported AEs in the Augmentin XR group were: diarrhea (20.3%), nausea (5.1%) and headache (4.5%). The most frequently reported AEs for patients who received either levofloxacin or clarithromycin comparator were: diarrhea (7.3%), nausea (5.9%) and taste perversion (5.6%).

In the combined, controlled CAP studies, the most frequently reported AEs in either treatment group were diarrhea (Augmentin XR: 16.0%, All Comparators: 12.4%), headache (Augmentin XR: 3.5%, All Comparators: 3.9%), and nausea (Augmentin XR: 3.3%, All Comparators: 4.4%). In uncontrolled CAP Study 547, the most commonly reported AEs were also diarrhea (19.5%), headache (6.2%) and nausea (4.5%).
In controlled ABS Study 550, the most common AEs reported in the Augmentin XR group were: diarrhea (26.9%), nausea (6.1%) and genital moniliasis (4.2%). The most frequently reported AEs by preferred term in the levofloxacin comparator group were: diarrhea (8.3%), nausea (5.6%) and injury (2.8%). In uncontrolled ABS Study 551, the most commonly reported AE was diarrhea (16.4%), followed by nausea (2.9%) and injury (2.8%).

Overall, the AE profiles were similar in Augmentin XR-treated patients across the — indications examined herein. However, as expected by the sample sizes and inherent variability of event rates, there was some fluctuation in the frequency of individual AEs by indication.

Generally, no marked differences were noted in the frequencies of F2F3-flagged hematology and/or clinical chemistry values between the Augmentin XR and All Comparators groups at the end of therapy in the combined controlled studies or in the controlled studies by indication. Within the CAP indication, a rise in platelets was seen over the course of the controlled and uncontrolled studies in both the Augmentin XR and All Comparators groups. Given that elevation of platelet count is a recognized response in CAP patients during recovery, these proportions (range: 4.5% to 11.8%) of patients with elevated platelets were not considered to be clinically significant. In combined controlled CAP studies there were two patients who reported an adverse experience (AE) of thrombocythemia (in the All Comparators group), neither of whom had an F2F3-flagged elevated platelet value. In uncontrolled CAP Study 547, eight patients reported an AE of thrombocythemia; seven of whom had F2F3-flagged elevated platelet values.

Safety Data From Ongoing Studies

No clinical pharmacology studies were ongoing at the time of data cut-off for serious AEs and deaths (31 August 2000).

At the time of data cut-off for serious AEs and deaths (31 August 2000), two clinical studies were ongoing, CAP Study 547 and CAP Study 557.

Study 547 is an uncontrolled, non-comparative, multicenter study to assess the efficacy and safety of oral Augmentin XR 2000/125mg twice daily for 7 days for the treatment of CAP in adults. A total of 310 patients were enrolled or completed after 19 June 2000, the cut-off for the prospectively defined interim analysis, through 31 August 2000. Twenty-six patients (8.4%) reported at least one serious AE. Thirty serious AEs were reported with pneumonia being the most frequently reported serious AE. Seven patients experienced serious AEs which resulted in death. Serious AEs leading to death were pneumonia (two patients), tuberculosis, cerebral stroke, pulmonary carcinoma, adenocarcinoma and unspecified death. All serious AEs leading to death were reported by the investigator as not related or unlikely to be related to Augmentin XR.

Study 557 is a controlled, active comparator study to assess the efficacy and safety of Augmentin XR 2000/125mg twice daily versus Augmentin 875/125mg tid for 7 or 10 days in the treatment of patients with CAP. Data from this study remain blinded. A total of 273 patients were randomized to this study as of 31 August 2000. Thirty-two patients (11.7%) reported a total of thirty-four serious AEs. Pneumonia was again the most frequently reported serious AE. No deaths occurred in this study as of the clinical data cut-off.

SAFETY CONCLUSIONS

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

This Integrated Summary of Safety (ISS) includes 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, this ISS contains 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 are 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 [redacted]. 33.0% for CAP and 41.9% for ABS. Exposure to Augmentin XR varied by indication. Mean exposure was 7.2 days in the [redacted] 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 III 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 can be summarized as follows:

- Augmentin XR was generally well-tolerated in the three completed Clinical Pharmacology studies and in the controlled and uncontrolled Phase III 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 b.i.d. 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 the 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 III 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 III studies, and those within 30 days of the cessation of therapy occurred 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.