# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 50-785

## CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

## CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA number:** | 50-785 |
| **Submission date:** | December 20, 2000 |
| **Product:** | 1000 mg amoxicillin/62.5 mg clavulanate potassium |
| **Dosage Form:** | Tablet (immediate release layer + sustained release layer) |
| **Trade name:** | Augmentin XR Tablet |
| **Sponsor:** | GlaxoSmithKline |
| **Type of submission:** | Original New Drug Application |
| **Reviewer:** | Jenny J Zheng, Ph.D. |

## I. EXECUTIVE SUMMARY

The sponsor developed a new formulation (Augmentin XR), which contains 1000 mg amoxicillin and 62.5 mg clavulanate in ratio of 16 to1, for treatment of [redacted], acute bacterial sinusitis (ABS), and community-acquired pneumonia (CAP).

Two Augmentin tablet formulations are currently on the market, which are amoxicillin 500 mg /clavulanate 125 mg (4:1) and amoxicillin 875mg/clavulanate 125 mg (7:1). Augmentin suspension (amoxicillin [redacted] mg /clavulanate [redacted] mg (14:1)) was recently approved for treatment of otitis media (OM).

Augmentin XR Tablet is composed of 1 immediate release layer [redacted] and 1 sustained release layer [redacted]

Three clinical pharmacokinetics studies were conducted with the Augmentin XR tablet to characterize the relative bioavailability (Study 558), food effect (Study 553), and drug interaction with Maalox (Study 583)). The results showed that the mean duration when amoxicillin concentration is above MIC (T>MIC), for an MIC of 4 μg/mL, was 6 and 4.9 hours for Augmentin XR and combination of immediate release formulations, respectively. It needs to be noted that T>MIC has been associated with the efficacy of amoxicillin in some clinical indications. When the systemic exposure to both amoxicillin and clavulanate is taken into consideration, Augmentin XR is optimally administered at the start of meal. The total exposure was not affected when Augmentin XR was taken with Maalox.

**COMMENTS:**

1. Although the new formulation was developed for sustained release, the pharmacokinetic properties of this new formulation do not allow for reducing the frequency of the dosing. The name of Augmentin XR may not be appropriate.
2. The dissolution specification for amoxicillin is recommended to be:
   Not less than [redacted] and not more than [redacted] in one hour
   Not less than [redacted] and not more than [redacted] in three hour
   Not less than [redacted] in five hour
3. The dissolution specification of clavulanate is recommended to be not less than [redacted] (Q) of the labeled amount of $C_8H_9NO_5$ to be dissolved in 30 minutes.

4. The standard meals used in bioavailability studies should be described in terms of calories, protein, fat, and carbohydrate content. The information should be included in the label.

**RECOMMENDATION:**
The studies are acceptable from clinical pharmacology point of view. Please convey the Comments to the sponsor.

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Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT initiated by F. PELSOR, Pharm.D., Team Leader _____

cc:
HFD-880 (Division File; F. Pelsor, TL)

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## II. TABLE OF CONTENTS

## III. Summary of clinical pharmacology and biopharmaceutics findings

The sponsor developed a modified release Augmentin formulation for treatment of infections caused by penicillin resistant *Streptococcus pneumoniae* (PRSP). A formulation containing 1 immediate release layer [redacted] and 1 sustained release layer [redacted] was found to be the most robust one to achieve the goal that the duration of time above MIC, for an MIC of 4 μg/mL, was more than 40% of dosing interval. Three clinical pharmacology studies were conducted to characterize the pharmacokinetics of Augmentin XR. It was found that a high fat meal increased systemic exposure to amoxicillin but decreased the systemic exposure to clavulanate. Therefore, when the total exposure of amoxicillin and clavulanate are considered, it is recommended the Augmentin XR be taken with a standard meal. The mean Cmax of amoxicillin is 17.0 μg/mL when Augmentin XR is given with a meal. The mean time above MIC, for an MIC of 4 μg/mL, is about 6 hours. Co-administration of Augmentin XR with Maalox does not affect the exposure to amoxicillin and clavulanate.

A three point dissolution test is proposed for Augmentin XR tablet.

## IV. Question based review

**What are the proposed indications?**

Augmentin XR is indicated for [redacted] acute bacterial sinusitis (ABS), and community-acquired pneumonia (CAP). Five clinical studies were conducted to evaluate the efficacy of Augmentin XR.

| [redacted] | Study 550 |
|---|---|
| ABS | Study 546 and 556 |
| CAP | Study 548, 549 |

In addition, two open-labeled, uncontrolled studies were conducted: Study 551 for ABS and Study 547 for CAP. In all studies Augmentin XR was administered at a dose of 2 tablets (2000/125mg) twice daily (total daily doses: 4000 mg amoxicillin and 250 mg clavulanate).

**What are the proposed dosage regimens?**

Augmentin XR will be taken orally. The proposed dose regimen for each indication is:

| [redacted] | |
|---|---|
| ABS | bid for 10 days |
| CAP | bid for 7-10 days |

**What are the characteristics of the exposure-response relationships for efficacy and safety?**

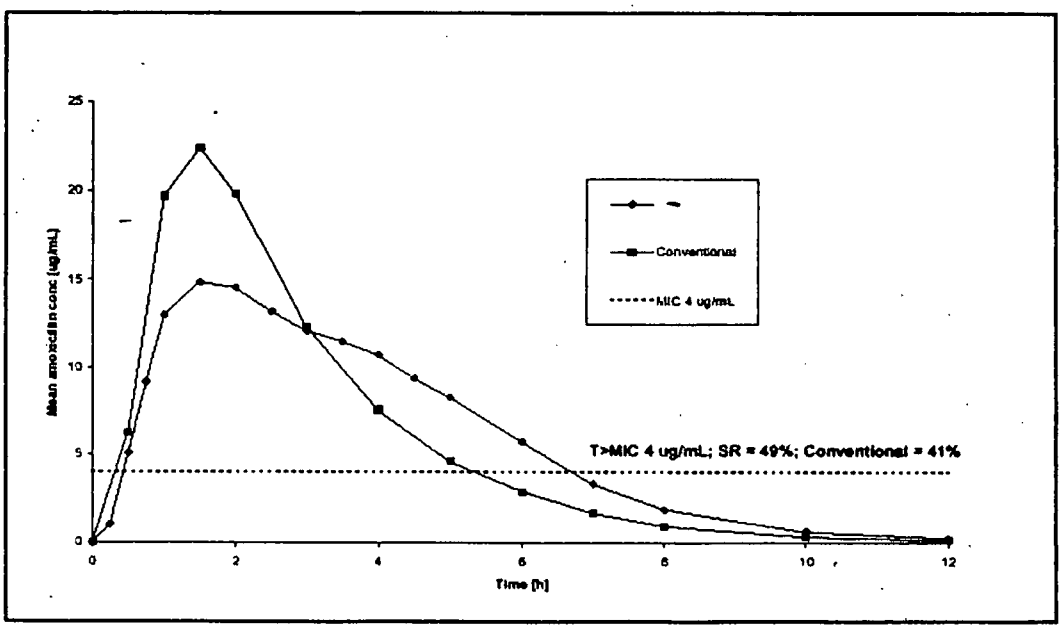
No PK/PD relationship study was conducted for this application. However, for β-lactam antibiotics it has been shown that achieving a time above MIC of approximately 40% or more of a dosing interval is indicative of therapeutic efficacy. The mean plasma

concentration-time profile for amoxicillin after Augmentin XR showed an initial peaking of amoxicillin concentrations followed by the suggestion of the presence of a secondary absorption phase arising from the sustained release component (Figure 1). Maximum plasma concentrations corresponded to the immediate release component and were observed at around 1 to 1.5 hours after dosing, similar to conventional Augmentin. The sustained plasma concentrations pooled from the three pharmacokinetic studies resulted in an average T>MIC for an MIC of 4 μg/mL exceeding 49% (95% CI: 47%, 52%) of the 12 hour dosing interval thus, predicting efficacy when pathogen MIC values are 4 ug/mL or lower. In a conventional Augmentin plus three amoxicillin immediate release tablets for a total amoxicillin dose of 2 g in study 558, Augmentin XR consistently achieved an amoxicillin T>MIC for an MIC of 4 ug/mL exceeding >40% of the dosing interval, whereas this was not the case for conventional Augmentin (95% CIs 42%-57% and 34%-48%, respectively).

Pooling all the data from three studies (N=52), the mean T>MIC for an MIC 2 μg/mL and 4 μg/mL are 7.2 and 5.9 hours, which corresponds to 60% and 49% of dose interval, respectively (N=55, 3 subjects had the same two treatments). After giving a single dose of Augmentin XR, 98% and 83% of the subjects had concentrations above 2 μg/mL and 4 μg/mL, respectively for more than 40% of the dose interval. In comparison, following administration of the approved Augmentin tablet (875 mg amoxicillin/125 mg clavulanate, 7:1) the mean T>MIC for an MIC of 2 μg/mL and 4 μg/mL were calculated using the data from NDA 50,720. The results showed that concentration was above MIC of 2 μg/mL and MIC of 4 μg/mL for about 5 and 3.6 hours, respectively. These values correspond to 42% and 30% of dose interval, respectively.

From a pharmacokinetics/pharmacodynamics point of view, Augmentin XR will provide better exposure especially for organisms with MIC of 4 μg/mL. However, it is not clear that the same T> MIC is needed for susceptible organisms (MIC= 2 μg/mL) compared to "resistant" organisms (MIC = 4 μg/mL) in order to show effectiveness.

**Figure 1. Mean plasma concentration-time profile for amoxicillin following oral administration of Augmentin XR and of conventional Augmentin (500/125 mg) plus 1.5 g amoxicillin**



**What are the pharmacokinetic properties of Augmentin XR?**

1. This formulation is designed to deliver amoxicillin from an immediate release layer and an extended release layer. The pharmacokinetics of amoxicillin should appear to be the same as following administration of an immediate release tablet after amoxicillin is absorbed. Therefore, the use of Augmentin XR in special populations should be the same as the approved conventional tablet (amoxicillin 500mg/clavulanate 125 mg (4:1) and amoxicillin 875 mg/ — mg clavulanate — (8:1))
2. Since clavulanate ——————————, as demonstrated by the results, its pharmacokinetic properties are similar to that of approved immediate release tablets.
3. Co-administration of Augmentin XR with a high fat meal appears to increase amoxicillin AUC but decrease clavulanate AUC, however, co-administration with a standard meal appears to increase amoxicillin AUC but does not change the clavulanate AUC. Therefore, Augmentin XR is recommended to be taken with a standard meal.
4. The pharmacokinetic parameters combining all the pharmacokinetic data from three studies when Augmentin XR was taken with a standard meal are shown in Table 1. The concentrations vs. time profiles for amoxicillin and calavulanate are shown in Figures 2 and 3.
5. Taking Augmentin XR with Maalox will not affect both amoxicillin and clavulanate exposure.

**Table 1. Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of *TRADENAME* to Healthy Adult Volunteers [n=55]**

| Parameter (units) | Amoxicillin | Clavulanate |
|---|---|---|
| AUC(0-inf) (ug.h/mL) | 71.6 (16.5) | 5.29 (1.55) |
| $C_{max}$ (ug/mL) | 17.0 (4.0) | 2.05 (0.80) |
| $T_{max}$ (hours)† | 1.50 — | 1.03 — |
| $T_{1/2}$ (hours) | 1.27 (0.20) | 1.03 (0.17) |
| T>MIC 4 ug/mL (hours) | 5.9 (1.2) | ND |
| T>MIC 4 ug/mL (% dosing interval) | 49.4 (10.2) | ND |

† median (range)
ND – not determined

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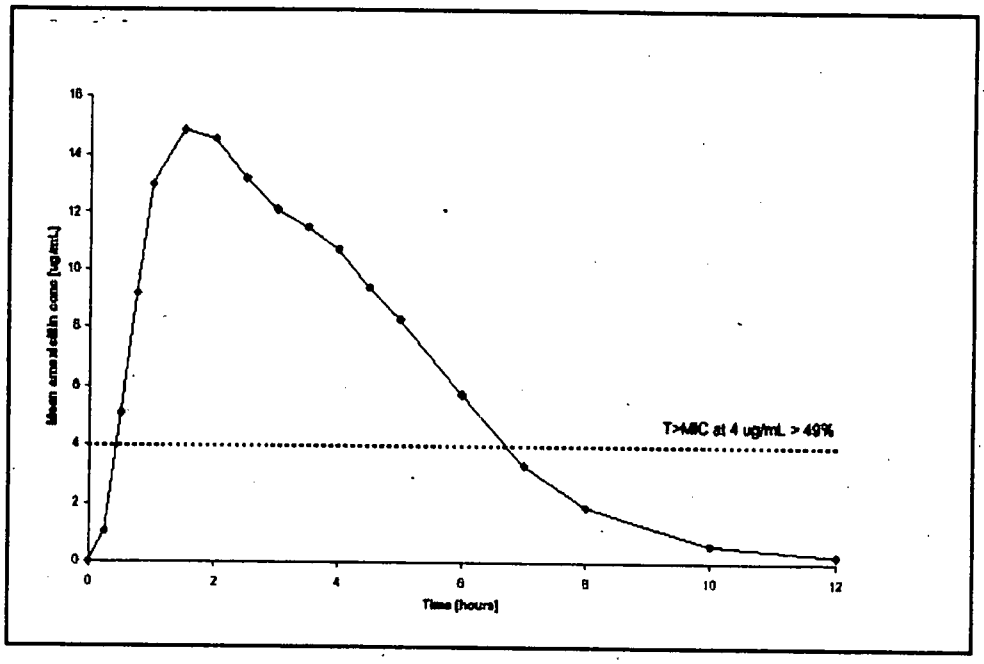
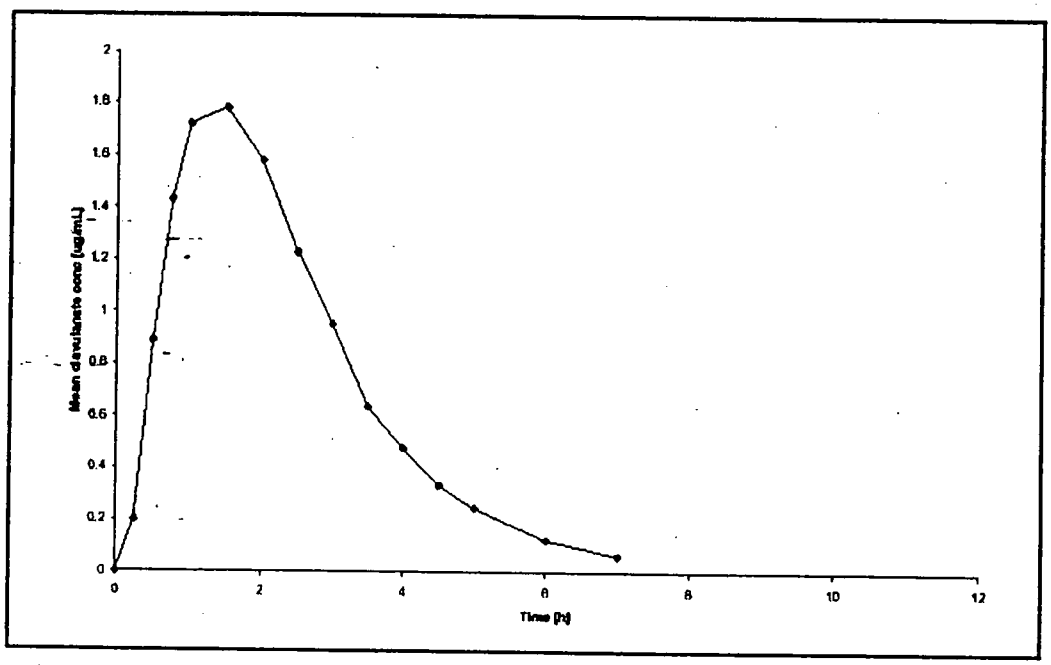
**Figure 2. Mean plasma concentration-time profile for amoxicillin following oral administration of Augmentin XR [n=55]**




n represents the total number of datasets

**Figure 3. Mean plasma concentration-time profile for clavulanate following oral administration of Augmentin — [n=55]**




n represents the total number of datasets

**Are the formulations used in the drug development program bioequivalent?**

Phase 1 vs. Phase 3: Three batches of Augmentin XR were produced for phase 3 studies. One batch in phase 3 was identical to that used in the Phase 1 "proof of concept" study, but two batches (B99015 and B99017) used in Phase 3 were different in that [redacted] was removed.

Phase 3 and to-be-marketed: The commercial formulation will contain the same level of [redacted] (identical to that for B99015 and B99017).

The compositions of the tablet are shown in Table 2.

**Table 2. Formulae for Tablets Used in Study 553, 583 and Phase III Studies**

| Name of Ingredient | Function | Quantity (mg/tablet) | | |
|---|---|---|---|---|
| | | FD-AA | FF-AA | FF-AB |
| | | B99012 | B99015 | B99017 |
| [redacted] | | | | |
| Amoxicillin Trihydrate | | [redacted] | | |
| Clavulanate Potassium | | | | |
| Microcrystalline Cellulose | | | | |
| Sodium Starch Glycollate | | | | |
| Colloidal Silicon Dioxide | | | | |
| Magnesium Stearate | | | | |
| [redacted] | | | | |
| [redacted] | | | | |
| Amoxicillin Sodium | | | | |
| Microcrystalline Cellulose | | | | |
| Xanthan Gum | | | | |
| Citric Acid | | | | |
| Colloidal Silicon Dioxide | | | | |
| Magnesium Stearate | | | | |
| [redacted] | | | | |
| **Total Weight of Tablet Core** | | | | |
| [redacted] Film Coat | | | | |
| **Total Weight of Coated Tablet** | | 1635.2 | 1635.2 | 1635.2 |

*: Equivalent to [redacted] mg of amoxicillin based on an assay of [redacted]

#: equivalent to [redacted] mg of clavulanic acid based on an assay of [redacted]

**: Equivalent to [redacted] mg amoxicillin based on an assay of [redacted]

**What are the dissolution conditions and specification?**

**Dissolution Test Conditions**

Apparatus: USP Apparatus 2 (Rotating Paddle)

Dissolution medium: 900 mL deionized water at 37 °C ± 0.5 °C

Paddle Speed: 75 rpm ± 4%

The dissolution tests were conducted in water, simulated gastric fluid and simulated intestinal fluid. It was found that it was necessary to use water as the medium as is the case with other amoxicillin clavulanate formulations because of instability of the amoxicillin and clavulanate at acid pH and in the presence of buffer salts.

**The proposed specification for amoxicillin:**

Not less than — in one hour: This provides control on the "Immediate Release" component. The limit takes account of the amount of the amoxicillin in the IR layer and the lower limit for amoxicillin content on the specification

Not more than — in two hours: The two-hour limit ensures that there is no "dose dumping" from the unit and that release is consistent with performance of tablets used in clinical programs.

Not less than — in five hours: This limit ensures that substantial release from the tablet occurs. It takes account of performance in biostudies, lower limits of amoxicillin content and the limits for content uniformity.

**Recommended dissolution specification by the reviewer:**

Not less than — and not more than — in one hour
Not less than — and not more than — in three hour
Not less than — in five hour

**Dissolution specification for clavulanate:**

Sponsor proposed: Not less than — in 1 hour

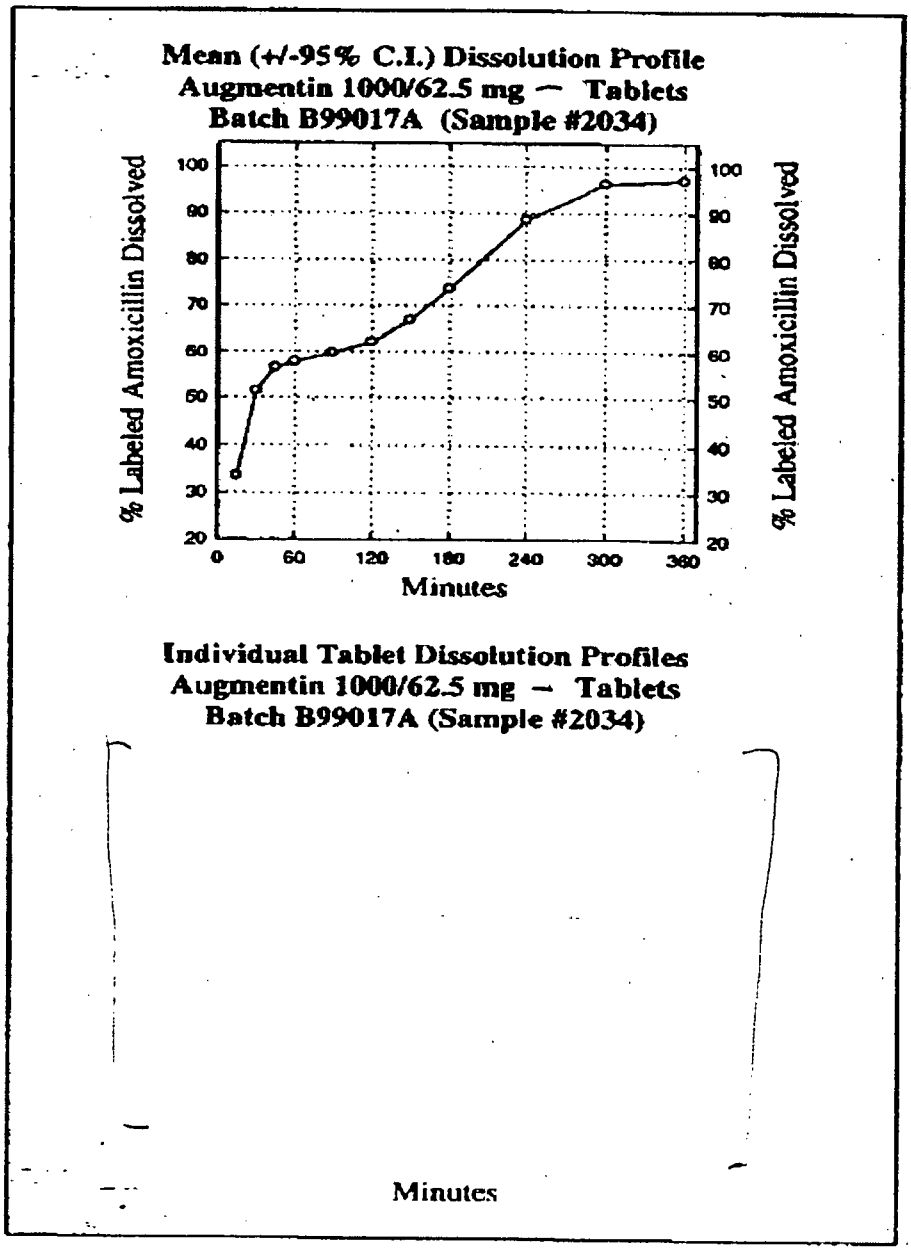
Reviewer proposed: To be consistent with IR tablet of 875 mg amoxicillin/ 125 mg clavulanate (7:1), the same specification is recommended. Not less than — (Q) of the labeled amount of $C_8H_9NO_5$ are dissolved in 30 minutes.

Sixteen tablets for each three batch were used in dissolution test. The mean release and (CV%) at 1, 2, 3 and 5 hours for the three batches are shown in the following table.

| | 1 hour | 2 hour | 3 hour | 5 hour |
|---|---|---|---|---|
| Batch 99012 | 59.44 (1.0) | 64.18 (1.0) | 79.70 (4.3) | 97.04 (1.0) |
| Batch 99015 | 59.12 (1.5) | 63.23 (1.4) | 74.01 (2.2) | 96.76 (1.5) |
| Batch 99017 | 57.88 (2.0) | 58.22 (26.8) | 73.58 (4.6) | 96.22 (1.4) |

The typical dissolution profiles for batch 99015 is shown in Figure 4.

Figure 4. A typical dissolution profiles




**Are analytical methods acceptable?**

Amoxicillin and clavulanate concentrations in plasma were measured by ———
The lower limit of quantification for amoxicillin was — ng/mL. The validation data showed that accuracy and precision of the assay are within ——

## V. Labeling recommendation:

The additions to the sponsor's draft are indicated by underline and deletions are indicated by strikeout. The **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** sections should read as follows:

**CLINICAL PHARMACOLOGY**

[

]

Amoxicillin systemic exposure achieved with ——— is similar to that produced by the oral administration of equivalent doses of amoxicillin. The pharmacokinetics of ——— were compared when — administered — at the start of a standardized meal ———— , or 30 minutes after a high-fat meal. When the systemic exposure to both amoxicillin and clavulanate is taken into consideration, ——— is optimally administered at the start of a —— meal. ——— ———— . The pharmacokinetics of the components of ——— following administration ——— at the start of a —— meal are presented below:

**Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of ——— to Healthy Adult Volunteers [n=55]**

| Parameter (units) | Amoxicillin | Clavulanate |
|---|---|---|
| AUC(0-inf) (ug.h/mL) | 71.6 (16.5) | 5.29 (1.55) |
| $C_{max}$ (ug/mL) | 17.0 (4.0) | 2.05 (0.80) |
| $T_{max}$ (hours)† | 1.50 (1.00-6.00) | 1.03 (0.75-3.00) |
| $T_{1/2}$ (hours) | 1.27 (0.20) | 1.03 (0.17) |
| ——— | — | — |
| ——— | ——— | — |

† median (range)

———

———

———— The half-life of amoxicillin after the oral administration of ——— is approximately 1.3 hours, and that of clavulanate is approximately 1.0 hour.

———

———

———

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

In a study in adults, the pharmacokinetics of amoxicillin and clavulanate were not affected by administration of an antacid (Maalox®), either simultaneously with or two hours after [redacted]
Neither component in [redacted] is highly protein-bound; clavulanate has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.
Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

**DOSAGE AND ADMINISTRATION**

[redacted] should be taken at the start of a [redacted] meal to enhance the absorption of [redacted] and to minimize the potential for gastrointestinal intolerance.

The recommended dose of [redacted] is 4000 mg/250 mg daily according to the following table:

| Indication | Dose | Duration |
|---|---|---|
| ABS | 2 tablets q12h | 10 days |
| [redacted] | [redacted] | [redacted] |
| CAP | 2 tablets q12h | 7-10 days |

**Renally impaired patients:** [redacted] renal impairment. [redacted] is contraindicated in severely impaired patients with a [redacted] of <30 mL/minute and in hemodialysis patients (See CONTRAINDICATIONS [redacted]

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

**Pediatric Use:** Safety and effectiveness in pediatric patients below the age of [redacted] have not been established.

**Geriatric Use:** No dosage adjustment is required for the elderly (see PRECAUTIONS).

## VI. Appendices

A. **Proposed package insert (original and Annotated)**

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Draft

Labeling

## B. Individual study review

**STUDY NUMBER:** 558
**TITLE:** An open randomised four part crossover study to investigate the relative bioavailability of three new sustained release — formulations of Augmentin in comparison to the standard immediate release (IR) formulation of Augmentin in healthy volunteers.
**INVESTIGATOR(S) AND CENTRE(S)**
Dr. O. Dewit, MD, MSc, PhD Clinical Pharmacology Unit, SmithKline Beecham Pharmaceuticals, New Frontier Science Park, (South), Third Avenue, Harlow, Essex, CM19 5AW, UK.
**OBJECTIVE(S):** To assess amoxicillin and clavulanate pharmacokinetics of three new sustained release — formulations on Augmentin in comparison with standard immediate release (IR) amoxicillin (Amoxil) and Augmentin tablets in healthy volunteers.
**STUDY DESIGN:** This study was conducted as an open randomized four part crossover study in twelve healthy subjects. Each subject received a single dose of the reference formulation and two of the three novel sustained release formulations. Each subject underwent four dosing sessions separated by at least three days. Each subject initially received a single dose of the reference formulation. After an adequate time period a dose of one of the three novel formulations was then administered. Again after an adequate time period a dose of another new formulation was administered. Finally each subject received a single dose of the second novel formulation (i.e. same formulation as in session 3). This regimen allowed for each novel formulation to be received by eight subjects and twice by four of the subjects hence allowing the estimation of intra-subject variability.

| | |
|---|---|
| Formulation A | 2 tablets containing a total of — mg amoxicillin trihydrate and 125 mg clavulanate — mg — **sodium amoxicillin** — — formulated with — **xanthan gum** and — citric acid. Batch B99012. |
| Formulation B | 2 tablets containing a total of — mg amoxicillin trihydrate and 125 mg clavulanate — mg — sodium amoxicillin — — formulated with — citric acid. Batch B99011. |
| Formulation C | 2 tablets containing a total of — mg amoxicillin trihydrate and 125 mg clavulanate — mg — — formulated with — xanthan gum and — citric acid. Batch B99010. |
| Formulation D *Reference* | One 500/125 Augmentin Tablet Batch B98002 and three 500mg Amoxil Tablets Batch KW2093. |

[ ]

The drug was given at the start of a standard meal (150 mls orange juice, tea/coffee, two slices of toast with butter, cereal with full fat milk)
**SAMPLING**: Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours after the dose.

**ASSAY:** The plasma samples were assayed for amoxicillin and clavulanate by [redacted] analysis.

**DATA ANALYSIS:**

Pharmacokinetics: Cmax and T>MIC of amoxicillin, at an MIC of 4 μg/mL were analyzed from plasma concentration-time data for each subject in each regimen. AUC(0-inf), Tmax, and $T_{1/2}$ were also determined for amoxicillin and for clavulanate as well as clavulanate Cmax. Amoxicillin T>MIC was calculated manually by graphical interpolation.

Statistics:

Amoxicillin Cmax, following log (base e)-transformation, and T>MIC were separately analysed by fitting a mixed effects model, with fixed effects sequence, period and regimen (A, B, C & D) and random effects subject(sequence). Point estimates for the least-squares means were calculated for each formulation, with accompanying 95% confidence intervals.

Within-subject coefficients of variation for Cmax, following log e -transformation, and T>MIC were calculated. Three separate analysis of variance models were produced for the replicate data of formulation A (from sequences DBAA and DCAA), formulation B (from sequences DABB and DCBB) and formulation C (from sequences DACC and DBCC), respectively. Terms in each model were fitted for subject and period (3 or 4).

**RESULTS:**

Twelve subjects were included in the study. One subject (005) was withdrawn after completing the first two parts (Regimens D and B). All other subjects completed all 4 parts.

The pharmacokinetic parameters, based on evaluable data from 12 subjects, are summarized in Table 1 and 2 for both amoxicillin and clavulanate (arithmetic means and SD, except Tmax values which are summarized by medians and ranges). The concentration vs time profiles for amoxicillin and clavulanate are shown in Figures 1 and 2. Values for the reference formulation (D) were low due to the samples being stored at an inappropriate temperature of –20°C for a period of time before assay. In contrast, amoxicillin is known to be stable in human plasma stored at -70 °C and through three freeze/thaw cycles, and so amoxicillin concentrations measured in samples collected after administration of formulation D would not have been affected by storing them at -20°C rather than at –70°C (SmithKline Beecham data on file).

Mean AUC(0-inf) values for clavulanate were similar across formulations A, B and C. A similar pattern across formulations also arose with the arithmetic mean Cmax values for clavulanate. The results of the statistical analysis are summarized in Table 3.

**CONCLUSION:**

Novel formulation A was superior to the other formulations in robustly achieving both the targets of least square mean Cmax of amoxicillin of 16 ug/mL or more, and a least square mean T>MIC of 4.8 hours (40% of a dosing interval) or more.

**Table 1. Pharmacokinetic parameter estimates for amoxicillin**

| Parameter | | Cmax (ug/mL) | Tmax* (h) | AUC(0-inf) (ug.h/mL) | T1/2 (h) | T>MIC (h) | T>MIC (%) |
|---|---|---|---|---|---|---|---|
| **Formulation A** | **Mean** | 17.4 | 1.75 | 75.6 | 1.32 | 6.0 | 50 |
| | **(SD)** | (1.95) | | (18.7) | (0.25) | (1.3) | (11) |
| **Formulation B** | **Mean** | 17.4 | 1.52 | 70.7 | 1.25 | 5.9 | 49 |
| | **(SD)** | (6.10) | | (25.4) | (0.15) | (1.3) | (10) |
| **Formulation C** | **Mean** | 20.5 | 2.13 | 71.4 | 1.21 | 5.1 | 42 |
| | **(SD)** | (7.61) | | (22.8) | (0.09) | (1.0) | (9) |
| **Formulation D** | **Mean** | 23.8 | 1.50 | 69.5 | 1.33 | 4.9 | 41 |
| | **(SD)** | (5.73) | | (15.6) | (0.16) | (1.0) | (8) |

*median and range

**Table 2. Pharmacokinetic parameter estimates for clavulanate**

| Parameter | | Cmax (ug/mL) | Tmax* (h) | AUC (0-inf) (ug.h/mL) | T1/2 (h) |
|---|---|---|---|---|---|
| **Formulation A** | **Mean** | 1.99 | 1.02 | 5.43 | 1.06 |
| | **(SD)** | (0.58) | | (1.24) | (0.143) |
| **Formulation B** | **Mean** | 1.88 | 1.66 | 5.18 | 1.03 |
| | **(SD)** | (0.58) | | (1.49) | (0.079) |
| **Formulation C** | **Mean** | 2.27 | 1.40 | 5.84 | 1.00 |
| | **(SD)** | (0.32) | | (0.89) | (0.10) |
| **Formulation D** | **Mean** | 1.00 | 1.26 | 2.47 | 1.06 |
| | **(SD)** | (0.38) | | (0.89) | (0.07) |

**Table 3. Least square means and 95% confidence intervals for Cmax and T>MIC for amoxicillin**

| Parameter | Formulation A | Formulation B | Formulation C | Formulation D |
|---|---|---|---|---|
| **Cmax[1] (ug/mL)** | 17.7 | 15.7 | 18.9 | 23.1 |
| | (14.3 , 22.0) | (12.8 ,19.3) | (15.4 , 23.1) | (19.0 , 28.0) |
| **T>MIC[1] (h)** | 5.9 | 6.2 | 5.0 | 4.9 |
| | (5.0 , 6.8) | (5.3 , 7.1) | (4.1 , 5.8) | (4.1 , 5.7) |

**Figure 1. Mean amoxycillin plasma profiles for study 25000/558**

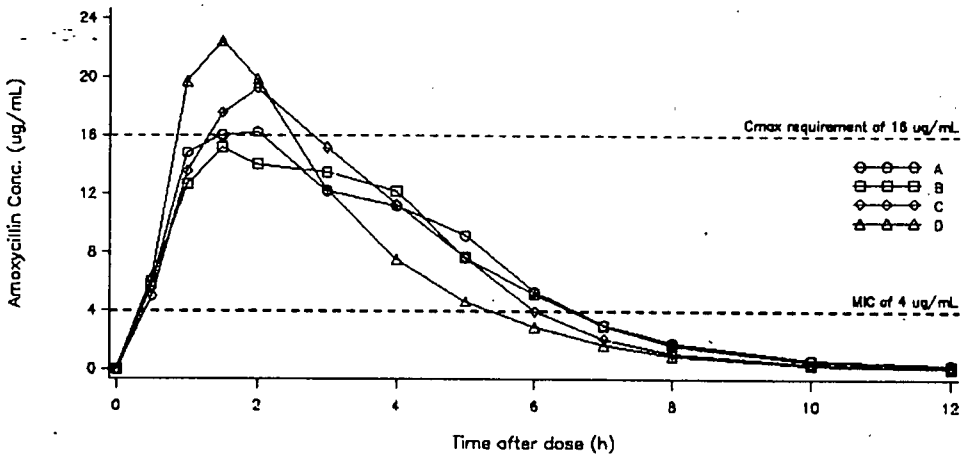
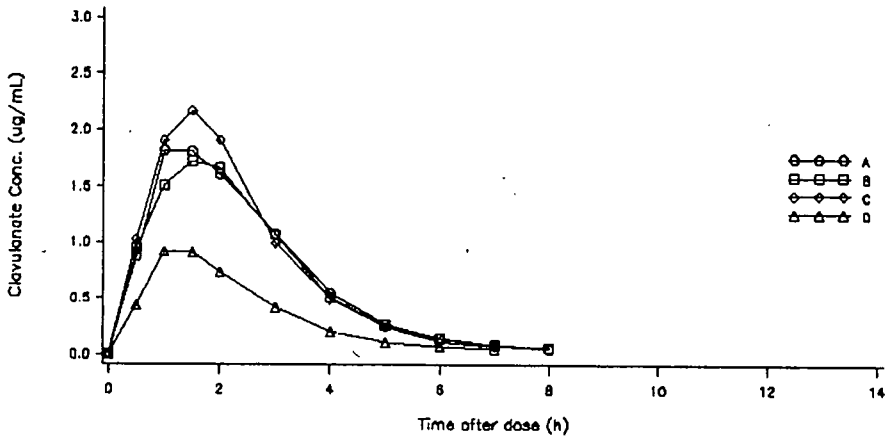



**Figure 2. Mean clavulanate plasma profiles for study 25000/558**

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**STUDY NUMBER:** 553

**TITLE:** An open, randomised, balanced, three period, single dose crossover study to investigate the effect of food on the bioavailability of sustained release oral Augmentin in healthy male and female volunteers.

**INVESTIGATOR(S) AND CENTRE(S)**

Dr. O. Dewit, MD, MSc, PhD Clinical Pharmacology Unit, SmithKline Beecham Pharmaceuticals, UK.

**OBJECTIVE(S):** To assess amoxicillin and clavulanate pharmacokinetic profiles from a sustained release formulation of Augmentin administered 30 minutes after the start of eating a recommended FDA high fat test meal and to compare them with those obtained when the dose was administered in the fasted state in healthy volunteers.

**STUDY DESIGN:** This study was an open, randomised, three period crossover design in healthy male and female volunteers.

Each volunteer participated in three sessions; each was administered a single oral dose of a sustained-release Augmentin XR formulation on three separate occasions, in randomised order. Subjects fasted overnight before receiving all three regimens.

**Treatment A:** Dose (Augmentin® — administered following an overnight fast (fasting from 10 pm the previous evening)

**Treatment B:** Dose (Augmentin® — administered exactly 30 minutes following the start of eating a recommended FDA high fat test meal which was consumed within twenty minutes.

**Treatment C:** Dose (Augmentin® — administered at the start of eating a standardised meal.

High fat meal: 2 strips bacon, grilled, 2 eggs cooked in butter, 2 slices of toast, 2 pats butter, 4 oz hash brown potatoes, 300 mL whole milk (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively).

Standardized meal: 150mls orange juice, tea/coffee, 2 slices of toast with butter, cereal with full fat milk.

**Formulation:** Each tablet contained: — mg amoxicillin trihydrate and 62.5 mg clavulanate ——— mg ——— sodium amoxicillin ——— formulated with — xanthan gum and — citric acid. White Tablet. (Batch. B99012)

**SAMPLING**: Blood samples were collected at pre-dose, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and 12 hours following the dose.

**ASSAY:** The plasma samples were assayed for amoxicillin and clavulanate by ——— analysis.

**DATA ANALYSIS:**

Pharmacokinetics: Cmax and T>MIC of amoxicillin, at an MIC of 4ug/mL were analysed from plasma concentration-time data for each subject in each regimen. AUC(0-inf), Tmax, and $T_{1/2}$ were also determined for amoxicillin and for clavulanate as well as clavulanate Cmax. For

amoxicillin the time above the minimum inhibitory plasma concentration (T>MIC) was calculated manually by graphical interpolation.

Statistics:

Following log-transformation (base e), AUC and Cmax were analysed separately by analysis of variance (ANOVA) fitting terms for sequence, subject (sequence), period and regimen. Point estimates and 90% confidence intervals of the difference were constructed for each comparison, using the residual variance. The point and interval estimates on the log e scale were then back transformed to give estimates of the ratio for each comparison. Tmax was analysed non-parametrically using the Wilcoxon matched-pairs method for each comparison of interest. A point estimate and 90% confidence interval for the median difference was constructed for each comparison. Assessment of T>MIC was made by way of descriptive statistics.

**RESULTS:**

The pharmacokinetic parameters and statistical analysis of amoxicillin and clavulanate are shown in Table 1 and 2. Systemic exposure to amoxicillin was higher when administered after a high fat meal compared to administration under fasted conditions (B:A), whilst it was lower in the fasted state compared to administration with a standardised meal (A:C). The extent of systemic exposure to amoxicillin after a high fat meal was slightly higher than with a standardized meal (B:C). Amoxicillin Cmax was similar across the three treatment regimens.

Systemic exposure to clavulanate was considerably lower when administered after commencement of a recommended FDA high fat test meal compared to administration under fasted conditions (B:A), and at the start of a standardised meal (B:C), whereas it was similar between the fasted state and administration of Augmentin XR at the start of a standardised meal (A:C). These changes in clavulanate AUC were also seen with clavulanate Cmax.

**CONCLUSION:**

1. Administration of Augmentin XR 30 minutes after the start of a recommended FDA high fat test meal, increased the extent of systemic exposure to amoxicillin and decreased the extent of systemic exposure to clavulanate compared to fasting conditions.
2. When the systemic exposure to both amoxicillin and clavulanate is taken into consideration Augmentin XR is optimally administered at the start of a standard meal.

**Table 1. Summary of amoxicillin and clavulanate pharmacokinetic parameters**

| | | Amoxicillin | | | Clavulanate | | |
|---|---|---|---|---|---|---|---|
| Parameter | Regimen | N | Arithmetic Mean | SD | N | Arithmetic Mean | SD |
| AUC(0-inf) (ug.h/mL) | A | 26 | 64.0 | 10.8 | 24 | 5.52 | 1.55 |
| | B | 25 | 87.0 | 10.8 | 26 | 4.22 | 1.66 |
| | C | 25 | 77.3 | 12.0 | 25 | 5.27 | 1.57 |
| AUC(0-t) (ug.h/mL) | A | 26 | 63.7 | 10.7 | 26 | 5.39 | 1.52 |
| | B | 26 | 85.5 | 9.88 | 26 | 4.12 | 1.66 |
| | C | 25 | 76.9 | 11.9 | 25 | 5.16 | 1.58 |
| Cmax (ug/mL) | A | 26 | 16.2 | 3.39 | 26 | 2.22 | 0.738 |
| | B | 26 | 16.8 | 2.91 | 26 | 1.52 | 0.664 |
| | C | 25 | 17.9 | 3.51 | 25 | 2.08 | 0.777 |
| Tmax* (hours) | A | 26 | 1.75 | | 26 | 1.50 | |
| | B | 26 | 2.50 | | 26 | 2.00 | |
| | C | 25 | 2.00 | | 25 | 1.00 | |
| T>MIC (hours) | A | 26 | 5.45 | 0.992 | NA | NA | NA |
| | B | 26 | 7.38 | 0.875 | | | |
| | C | 25 | 6.19 | 0.815 | | | |
| T>MIC (%) | A | 26 | 45.4 | 8.25 | NA | NA | NA |
| | B | 26 | 61.5 | 7.31 | | | |
| | C | 25 | 51.6 | 6.80 | | | |
| Parameter | Regimen | N | Geometric Mean | CVb (%) | N | Geometric Mean | CVb (%) |
| AUC(0-inf) (ug.h/mL) | A | 26 | 63.2 | 16.1 | 24 | 5.32 | 28.5 |
| | B | 25 | 86.3 | 12.5 | 26 | 3.90 | 43.1 |
| | C | 25 | 76.5 | 14.9 | 25 | 5.01 | 34.6 |
| AUC(0-t) (ug.h/mL) | A | 26 | 62.9 | 16.1 | 26 | 5.19 | 28.8 |
| | B | 26 | 84.9 | 11.6 | 26 | 3.79 | 44.6 |
| | C | 25 | 76.1 | 14.8 | 25 | 4.90 | 36.0 |
| Cmax (ug/mL) | A | 26 | 15.8 | 21.1 | 26 | 2.09 | 37.8 |
| | B | 26 | 16.5 | 17.4 | 26 | 1.37 | 51.8 |
| | C | 25 | 17.5 | 21.0 | 25 | 1.93 | 43.0 |

* median(range)

Regimen codes:

A : Augmentin® – fasted

B : Augmentin® – 30 mins following start of a high fat meal

C : Augmentin® – at the start of a standardised meal

*Tmax – median and range given

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**Table 2. Comparison between regimens for amoxicillin pharmacokinetic parameters**

| | | Amoxicillin | | Clavulanate | |
|---|---|---|---|---|---|
| **Parameter** | **Comparison** | **Point Estimate** | **90% C.I.** | **Point Estimate** | **90% C.I.** |
| AUC(0-inf) | B : A | 1.38 | 1.30 , 1.46 | 0.71 | 0.61 , 0.82 |
| | A : C | 0.83 | 0.78 , 0.88 | 1.08 | 0.93 , 1.25 |
| | B : C | 1.14 | 1.08 , 1.21 | 0.76 | 0.66 , 0.89 |
| AUC(0-t) | B : A | 1.35 | 1.28 , 1.43 | 0.72 | 0.62 , 0.83 |
| | A : C | 0.83 | 0.78 , 0.88 | 1.06 | 0.91 , 1.23 |
| | B : C | 1.12 | 1.06 , 1.19 | 0.76 | 0.65 , 0.88 |
| Tmax (hours) | B – A | 0.38 | -0.50 , 0.75 | 0.65 | 0.54 , 0.78 |
| | A – C | 0.02 | -1.02 , 0.25 | 1.08 | 0.89 , 1.30 |
| | B – C | 0.50 | -0.76 , 0.55 | 0.70 | 0.58 , 0.85 |
| Cmax | B : A | 1.05 | 0.97 , 1.15 | 0.99 | 0.50 , 1.01 |
| | A : C | 0.92 | 0.85 , 1.00 | 0.01 | -0.50 , 0.15 |
| | B : C | 0.97 | 0.89 , 1.06 | 1.00 | 0.25 , 1.24 |

A : Augmentin® – fasted

B : Augmentin® – 30 mins following start of a high fat meal

C : Augmentin® – at the start of a standardised meal

*Tmax – median and range given

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**Figure 1. Mean amoxicillin plasma concentrations (ug/mL) in healthy male and female subjects administered Augmentin –**

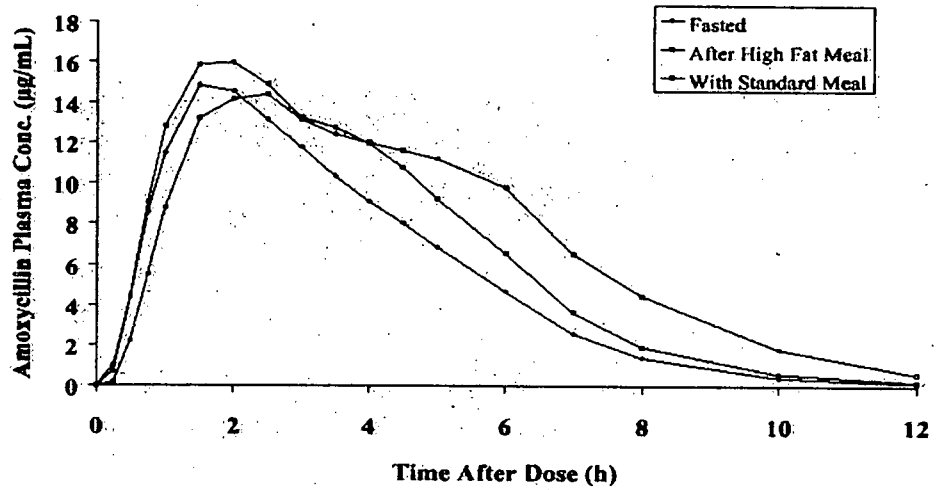
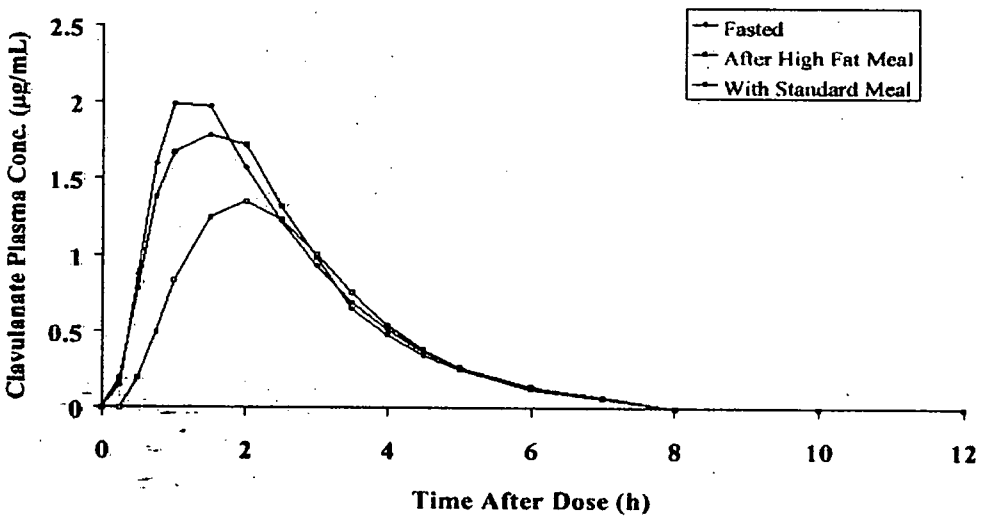



**Figure 2. Mean clavulanate plasma concentrations (ug/mL) in healthy male and female subjects administered Augmentin –**



**STUDY NUMBER:** 583

**TITLE:** An open, randomised, three way crossover study to investigate the effect of Maalox® on the bioavailability of sustained release oral Augmentin® (BRL 25000) in healthy male and female volunteers.

**INVESTIGATOR(S) AND CENTRE(S)**

Dr. O. Dewit, MD, MSc, PhD Clinical Pharmacology Unit, SmithKline Beecham, Pharmaceuticals, UK.

**OBJECTIVE(S):** To estimate the effect of the co-administration of Maalox® on the bioavailability of Augmentin XR.

To estimate the effect on the bioavailability of Augmentin XR of administering Maalox® two hours later.

**STUDY DESIGN:** This study was conducted as an open, randomised, three period crossover design in healthy male and female volunteers.

Each volunteer participated in three separate dosing sessions, in which each volunteer was administered a single oral dose of a sustained-release Augmentin formulation (Augmentin®, in randomised order, according to the following regimen:

Regimen A: Augmentin® administered two hours before Maalox®(20 mLs)

Regimen B: Augmentin® administered simultaneously with Maalox® (20 mLs)

Regimen C: Augmentin® administered alone

Augmentin® was administered as two tablets to be swallowed, without chewing, with 240 mL of water at room temperature at the start of eating a standard meal (150 mls orange juice, tea/coffee, 2 slices of toast with butter, cereal with full fat milk) following an overnight fast. The Maalox® suspension was administered orally via a 20 mL syringe.

For regimen B, Augmentin® was administered first, followed by Maalox® (20 mLs).

**FORMULATION:** Each tablet contained: mg amoxicillin trihydrate and 62.5 mg clavulanate mg sodium amoxicillin formulated with xanthan gum and citric acid. Batch, B99012.

**SAMPLING**: Blood samples were collected at pre-dose 15, 30 and 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10 and12 hours following dosing.

**ASSAY:** The plasma samples were assayed for amoxicillin and clavulanate by analysis.

**DATA ANALYSIS:**

Pharmacokinetics: Cmax and T>MIC of amoxicillin, at an MIC of 4ug/mL were analysed from plasma concentration-time data for each subject in each regimen. AUC(0-inf), Tmax, and $T_{1/2}$ were also determined for amoxicillin and for clavulanate as well as clavulanate Cmax. For

amoxicillin the time above the minimum inhibitory plasma concentration (T>MIC) was calculated manually by graphical interpolation, where the minimum inhibitory plasma concentration was defined as 4 ug/mL.

Statistics:

Following log-transformation (base e), AUC and Cmax were analysed separately by analysis of variance (ANOVA) fitting terms for sequence, subject (sequence), period and regimen. Point estimates and 90% confidence intervals of the difference were constructed for each comparison, using the residual variance. The point and interval estimates on the log e scale were then back transformed to give estimates of the ratio for each comparison. Tmax was analysed non-parametrically using the Wilcoxon matched-pairs method for each comparison of interest. A point estimate and 90% confidence interval for the median difference was constructed for each comparison. Assessment of T>MIC was made by way of descriptive statistics.

**RESULTS:**

The pharmacokinetic parameters of amoxicillin and clavulanate as well as statistical analysis are shown in Tables 1 and 2 for each treatment.

Mean plasma concentrations of amoxicillin following administration of Augmentin XR two hours before Maalox®, or administration of Augmentin simultaneously with Maalox®, were similar to those following administration of Augmentin — alone as shown in Figures 1 and 2.

**CONCLUSION:**

The administration of Maalox® simultaneously with Augmentin XR or two hours after Augmentin XR, had no effect on the pharmacokinetics of either amoxicillin or clavulanate.

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**Table 1. The pharmacokinetic parameters of amoxicillin and clavulanate**

| | | Amoxicillin | | | | | | Clavulanate | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Regimen | | AUC(0-inf) (ug.h/mL) | Cmax (ug/mL) | Tmax* (h) | T½ (h) | T>MIC (h) | T>MIC (%) | AUC(0-inf) (ug.h/mL) | Cmax (ug/mL) | Tmax* (h) | T½ (h) |
| A | Mean | 63.2 | 15.6 | 1.52 | 1.36 | 5.71 | 47.6 | 4.91 | 1.89 | 1.50 | 1.02 |
| | SD | 13.1 | 4.3 | — | 0.26 | 1.18 | 9.8 | 1.83 | 0.83 | — | 0.13 |
| | N | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| B | Mean | 62.8 | 16.2 | 1.52 | 1.31 | 5.31 | 44.3 | 5.27 | 2.00 | 1.00 | 1.04 |
| | SD | 18.8 | 5.8 | — | 0.18 | 1.38 | 11.5 | 1.66 | 0.78 | — | 0.13 |
| | N | 19 | 19 | 19 | 19 | 19 | 19 | 18 | 19 | 19 | 18 |
| C | Mean | 60.8 | 15.5 | 1.50 | 1.22 | 5.44 | 45.4 | 5.15 | 1.99 | 1.50 | 1.01 |
| | SD | 16.3 | 4.8 | — | 0.11 | 1.45 | 12.1 | 1.50 | 0.85 | — | 0.12 |
| | N | 20 | 20 | 20 | 20 | 20 | 20 | 19 | 20 | 20 | 19 |

Regimen codes:

A : Augmentin — administered two hours before Maalox®

B : Augmentin — administered simultaneously with Maalox®

C : Augmentin — administered alone

**Table 2. Statistical analysis on pharmacokinetic parameters of amoxicillin and clavulanate**

| | | Amoxicillin | | Clavulanate | |
|---|---|---|---|---|---|
| **Parameter** | **Comparison** | **Point Estimate** | **90% C.I.** | **Point Estimate** | **90% C.I.** |
| T>MIC [h] | A – C | 0.27 h | -0.34 , 0.89 | NA | NA |
| | B – C | -0.13 h | -0.75 , 0.48 | NA | NA |
| AUC(0-inf) | A : C | 1.07 | 0.93 , 1.24 | 0.97 | 0.87 , 1.09 |
| | B : C | 1.00 | 0.87 , 1.16 | 1.01 | 0.90 , 1.13 |
| Cmax | A : C | 1.05 | 0.95 , 1.15 | 1.01 | 0.84 , 1.21 |
| | B : C | 1.02 | 0.92 , 1.12 | 1.02 | 0.85 , 1.22 |
| Tmax [h] | A – C | -0.25 h | -0.99 , 0.26 | 0.00 | -0.25 , 0.48 |
| | B – C | 0.00 h | -0.25 , 0.39 | -0.12 | -0.26 , 0.03 |

**Figure 1. Mean amoxicillin plasma concentrations (ug/mL) in healthy male and female subjects administered Augmentin —**

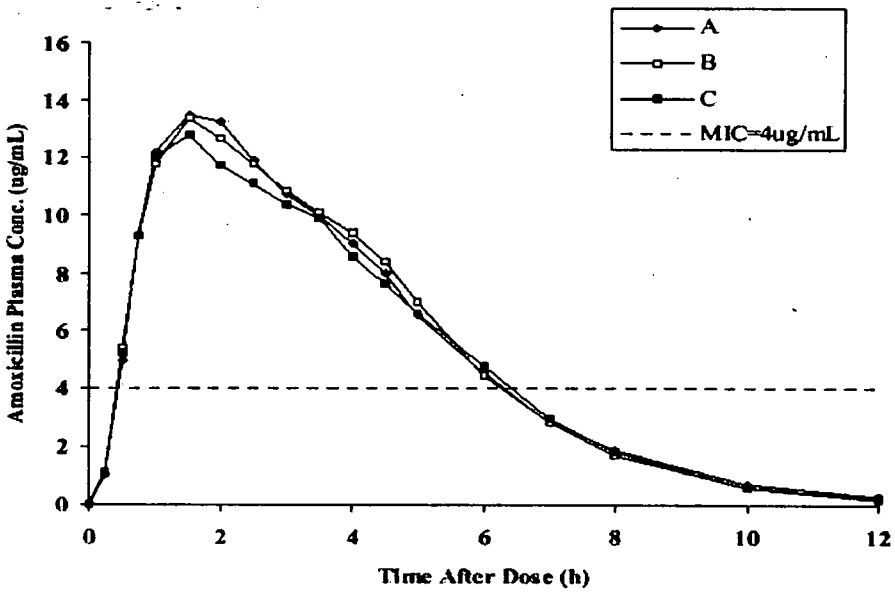
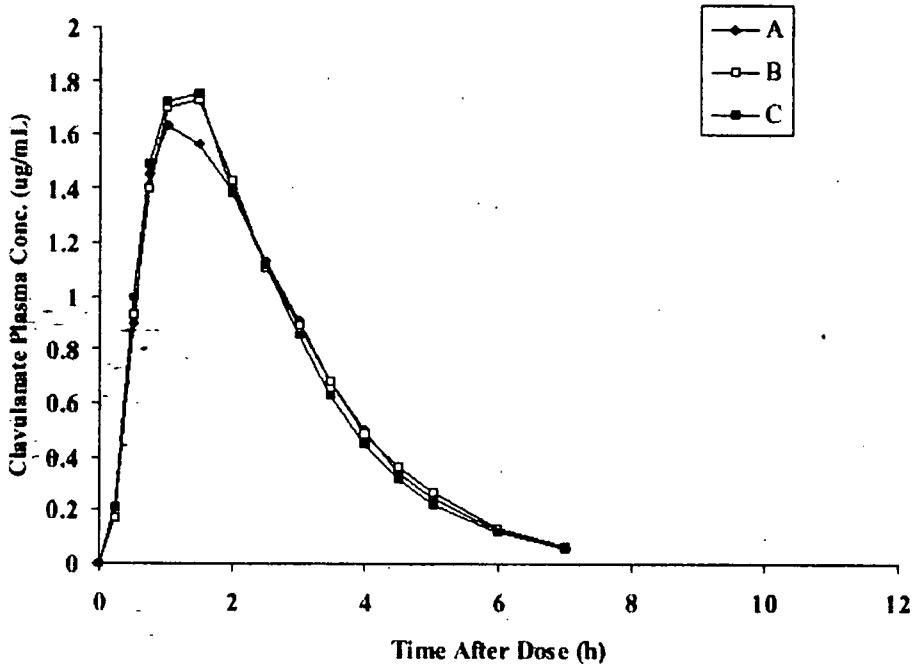



**Figure 2. Mean clavulanate plasma concentrations (ug/mL) in healthy male and female subjects administered Augmentin —**



**STUDY NUMBER:** 552
**TITLE:** A two-part crossover study to assess the pharmacokinetics of amoxicillin after administration with clavulanate of sustained release formulations of amoxicillin in healthy volunteers.
**INVESTIGATOR(S) AND CENTRE(S)**

[ ]

**OBJECTIVE(S):** To assess amoxicillin pharmacokinetics of sustained release formulations of amoxicillin when co-administered orally with an Augmentin tablet in healthy male and female volunteers.
To determine the combination which best meets the acceptance criteria for use in phase 3 clinical trials. The target PK values proposed include a mean T>MIC of amoxicillin at MIC of 4ug/mL to be at least 40% of the 12 h dosing interval (i.e. to be at least 4.8 hours) and a mean Cmax to be equal to or greater than 16ug/mL (4 times MIC of 4ug/mL).
**STUDY DESIGN:** This study was conducted as an open, two-part crossover study in 40 healthy subjects, divided in five subgroups of 8 subjects (4 males and 4 females) to allow for comparison of all 5 formulations versus reference formulation. Each subject participated in two dosing sessions, separated by at least three days. Each subject received a single dose of the reference formulation and was randomly assigned to receive a single dose of one novel formulation. Each dose was co-administered with an Augmentin tablet immediately preceding a light breakfast.
The formulation used in the study is shown in the following table:

| | |
|---|---|
| Formulation A | Sustained release [redacted] amoxicillin trihydrate [redacted] mg (B99005), formulated to [redacted] (approximately [redacted] xanthan gum), co-administered with an Augmentin tablet 875/125 (B98001/47289). |
| Formulation B | [redacted] amoxicillin trihydrate [redacted] mg (B99004), formulated to [redacted] (approximately [redacted] xanthan gum), co-administered with an Augmentin . tablet 875/125 (B98001/47289). |
| Formulation C | [redacted] sodium amoxicillin [redacted] mg (B99006), formulated to [redacted] [redacted] (approximately [redacted] xanthan gum), co-administered with an Augmentin . tablet 875/125 (B98001/47289). |
| Formulation D | [redacted] sodium amoxicillin [redacted] mg (B99008), formulated to [redacted] [redacted] (approximately [redacted] xanthan gum, [redacted] Citric acid), co-administered with an Augmentin tablet 875/125 (B98001/47289). |
| Formulation E | [redacted] sodium amoxicillin [redacted] mg (B99007), formulated to [redacted] [redacted] (approximately [redacted] xanthan gum), co-administered with an Augmentin . tablet 500/125 (B98002) and an Amoxil tablet 500mg (KW2093). |
| Formulation F *Reference* | One tablet of Amoxil 875mg (trihydrate amoxicillin, MD2408) and a tablet of Augmentin . 875/125 (B98001/47289). |

**SAMPLING**: Blood samples were collected for amoxicillin assay pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours after the start of dosing.
**DATA ANALYSIS:**
Pharmacokinetics: Cmax and T>MIC of amoxicillin, at an MIC of 4ug/mL were analyzed from plasma concentration-time data for each subject in each regimen. AUC(0-inf), Tmax, and $T_{1/2}$ were also determined for amoxicillin and for clavulanate as well as clavulanate Cmax. For amoxicillin the time above the minimum inhibitory plasma concentration (T>MIC) was calculated manually by graphical interpolation, where the minimum inhibitory plasma concentrations was defined as 4 ug/mL.
Statistics:

Following log-transformation (base e), AUC and Cmax were analysed separately by analysis of variance (ANOVA) fitting terms for sequence, subject(sequence), period and regimen. Point estimates and 90% confidence intervals of the difference were constructed for each comparison, using the residual variance. The point and interval estimates on the log e scale was then back transformed to give estimates of the ratio for each comparison. Tmax was analysed non-parametrically using the Wilcoxon matched-pairs method for each comparison of interest. A point estimate and 90% confidence interval for the median difference was constructed for each comparison. Assessment of T>MIC was made by way of descriptive statistics.

**RESULTS:**

The pharmacokinetic parameters and statistical analysis of amoxicillin are shown in Table 1 and 2. The target for Cmax and T>MIC with MIC=4 µg/mL are 16 µg/mL and 4.8 hours, respectively. The point estimate for formulation A was below the target criteria for both Cmax and T>MIC, while the 95% confidence interval does include the target for T>MIC. For formulation B, the entire 95% confidence interval exceeds the target criteria for Cmax of 16ug/mL, although the point estimate for T>MIC is below the target of 4.8 hours, but the target is included in the 95% confidence interval. For formulation C, the point estimate just exceeds the target for Cmax, but falls below for T>MIC. For formulation C the target is within the 95% confidence intervals for both parameters. Formulation D has the potential to deliver the greatest T>MIC values. For formulation D, the point estimate exceeds the target for T>MIC, but falls below for Cmax. The target values are within the 95% confidence intervals for both parameters. The variability observed with formulation D was notably higher than other formulations for T>MIC, although it was notably lower for Cmax. The point estimate for formulation E was just below the target criteria for Cmax and also below for T>MIC. The 95% confidence intervals for formulation E include the target for both parameters. These results need to be considered alongside the fact that formulation E contained only —mg amoxicillin. All five of the novel formulations had higher point estimates for T>MIC than the standard (F), which contained all immediate release amoxicillin.

**CONCLUSION:**

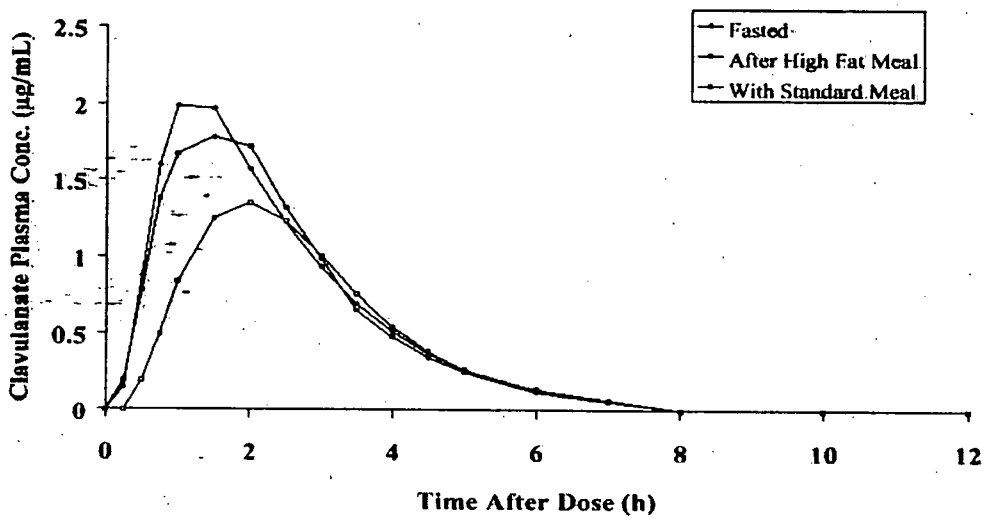
1. In terms of the **point estimates** achieved, none of the novel formulations attained both target criteria of Cmax =16ug/mL and T>MIC =4.8 hours.
2. Formulation D ( ——— sodium amoxicillin — mg, formulated to ———— (approximately — xanthan gum), coadministered with an Augmentin ® tablet 875/125) was the only formulation whose point estimate represented a substantial increase over the T>MIC target of 4.8 hours. At the same time, the 95% CI of its Cmax included the target of 16ug/mL.

**Table 1. Arithmetic Mean (SD) Pharmacokinetic Parameter Estimates for Amoxicillin [A-E n=8, F n=40]**

| | Formulation | | | | | |
|---|---|---|---|---|---|---|
| Parameters | A | B | C | D | E | F |
| T>MIC 4ug/mL (h) | 4.5 | 4.4 | 4.4 | 5.7 | 4.8 | 4.3 |
| | (1.8) | (0.7) | (0.9) | (2.5) | (0.9) | (0.8) |
| Cmax (ug/mL) | 12.8 | 23.8 | 18.6 | 13.0 | 17.3 | 20.2 |
| | (4.96) | (10.6) | (4.72) | (2.34) | (4.62) | (6.09) |
| Tmax (hours)* | 1.53 | 1.51 | 1.50 | 1.25 | 1.75 | 1.50 |
| | — | — | — | — | — | — |
| AUC(0-inf) (ug.h/mL) | 48.2 | 69.1 | 57.6 | 57.8 | 57.3 | 56.5 |
| | (24.0) | (24.3) | (15.3) | (25.0) | (9.0) | (16.1) |
| T1/2 (hours) | 1.42 | 1.23 | 1.29 | 1.93 | 1.44 | 1.31 |
| | (0.26) | (0.13) | (0.14) | (0.87) | (0.26) | (0.20) |

**Table 2. Point Estimates and 95% Confidence Intervals for Each Formulation**

| Parameter | Formulation | Point Estimate | 95% C.I. |
|---|---|---|---|
| Cmax (ug/mL) | A | 12.66 | (10.52, 15.24) |
| | B | 22.55 | (18.76, 27.10) |
| | C | 16.25 | (13.46, 19.63) |
| | D | 13.82 | (11.47, 16.65) |
| | E | 15.88 | (13.19, 19.10) |
| T>MIC (h) | A | 4.62 | (3.73, 5.50) |
| | B | 4.57 | (3.68, 5.45) |
| | C | 4.65 | (3.76, 5.54) |
| | D | 5.55 | (4.66, 6.43) |
| | E | 4.41 | (3.51, 5.30) |



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## CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA number:** | 50-785 |
| **Submission date:** | March 29, 2002 |
| **Product:** | 1000 mg amoxicillin/62.5 mg clavulanate potassium |
| **Dosage Form:** | Tablet (immediate release layer + sustained release layer) |
| **Trade name:** | Augmentin XR Tablet |
| **Sponsor:** | GlaxoSmithKline |
| **Type of submission:** | New Drug Application resubmission |
| **Reviewer:** | Jenny J Zheng, Ph.D. |

The sponsor originally submitted this NDA on December 20, 2000. The clinical division did not approve the application due to the lack of evidence to support the sponsor's claim that Augmentin XR is efficacious against penicillin resistant organisms. The sponsor re-submitted this NDA on March 29, 2002 with a new study in which more penicillin resistant *S. pneumoniae* (PRSP) were isolated in the trial. In the original submission, four pharmacokinetic studies were reviewed and found to be acceptable from the clinical pharmacology and biopharmaceutics perspective [see OCPB Review by Jenny J. Zheng, Ph.D.,12/12/02].

However, the Clinical Pharmacology and Biopharmaceutics reviewer recommended changes in the dissolution specification and several minor changes in the label. In this re-submission, no new pharmacokinetic study reports were submitted and the information contained in this Clinical Pharmacology and Biopharmaceutics review pertains to the review of dissolution and setting the dissolution specification for Augmentin XR Tablets. Furthermore, the sponsor provided an updated label for review.

**Dissolution specification for amoxicillin:**

The proposed dissolution specification for amoxicillin in the original submission was the following:

Not less than — in one hour
Not more than — in two hours
Not less than — in five hours

Recommended dissolution specification for amoxicillin by the reviewer after reviewing the original submission is as follows:

Not less than — and not more than — in one hour
Not less than — and not more than — in three hour
Not less than — in five hour

There were two significant changes in dissolution specification for amoxicillin:

1) a release window instead of a single value at 1 and 3 hour is recommended;
2) a 3 hour dissolution timepoint instead of a 2 hour timepoint is recommended. The reviewer believed that the 3 hour dissolution time point is more appropriate than the 2 hour dissolution time point because: i) the second peak in the amoxicillin plasma concentration vs. time profile, which reflects the absorption of amoxicillin from the sustained release layer, occurs at approximately — postdose, which is closer to the 3 hour-dissolution time point than the 2-hour time point and ii) the 2-hour

dissolution time point is in the relatively "flat" or "plateau" region of the dissolution profile when the release of amoxicillin from the sustained release layer has not yet started. In contrast, the 3-hour dissolution time point would more adequately reflect the release from the sustained release layer.

In the re-submission, the sponsor proposed the following dissolution specification:
NLT — and NMT — in 1 hour
NLT — and NMT — in 2 hour
NLT — in 6 hour
The justification of this new specification was that the sponsor believed that a 2 hour test point is a better control for the plateau in the dissolution profile that reflects the interval between dissolution of the immediate release component and initiation of the second phase of release. It also provides assurance against premature release from the sustained release layer. Instead, 3 hour test point in contrast falls on the ascending part of the second phase of release and because changes is more rapid at this stage, data are more variable and control limits need to be wider as a consequence.

It was observed by the reviewer that the high variability at 3 hour time point is the result of pooling data from the initial dissolution test with the stability data that included 12 month and 24 month stability data. It was observed that dissolution profiles are similar between the initial test and 12 month stability test, however, the profile changed for 24-month stability test. Compared with dissolution pattern for initial testing, the release from the sustained release layer for the 24-month stability batches was slower. The typical profiles are attached. The similarity factor (f2) between initial test and 12-month stability test was 72 and between initial test and 24-month stability test was 48. All the batches passed the dissolution specification recommended by the reviewer except the 24-month stability batches. The reviewer believed that the 3 hour time point should be used and the comment was conveyed to the sponsor. In response to the comment, the sponsor agreed to use 3 hour time point.

The recommended finial dissolution specification for the amoxicillin component of Augmentin XR Tablets is the following:
Not less than — and not more than — in one hour
Not less than — and not more than — in three hour
Not less than — in five hour

**Dissolution specification for clavulanate:**
The sponsor proposed dissolution specification for clavulanate was not less than — in 1 hour in the original submission. Because no data was submitted in the original submission, the reviewer recommended that, to be consistent with IR tablet of 875 mg amoxicillin/ 125 mg clavulanate (7:1), the same specification should be used which is not less than — (Q) of the labeled amount of clavulanate dissolved in 30 minutes. In the re-submission the sponsor submitted the dissolution data and the data were reviewed. It was recommended that dissolution specification should be not less than — in 1 hour for clavulanate.

**Recommended dissolution specification for amoxicillin and clavulanate for Augmentin XR Tablets:**

Amoxicillin:

Not less than — and not more than — in one hour
Not less than — and not more than — in three hour
Not less than — in five hour

Clavulanate:

The recommended dissolution specification for clavulanate is not less than — in 1 hour.

**LABELING RECOMMENDATION:**

The updated labeling was reviewed and the recommendations to the labeling changes are presented in the followings. The additions to the sponsor's draft are indicated by underline and deletions are indicated by strikeout. The **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** sections should read as follows:

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of *Augmentin XR*.

*Augmentin XR* is an extended-release formulation which provides sustained plasma concentrations of amoxicillin. Amoxicillin systemic exposure achieved with *Augmentin XR* is similar to that produced by the oral administration of equivalent doses of amoxicillin alone. —

In a — study — of healthy adult volunteers, the pharmacokinetics of *Augmentin XR* were compared when it was administered in a fasted state — at the start of a standardized meal (612 kcal, 89.3 g carb, 24.9 g fat, 14.0 g protein), or 30 minutes after a high-fat meal. When the systemic exposure to both amoxicillin and clavulanate is taken into consideration, *Augmentin XR* is optimally administered at the start of a standardized meal, — The pharmacokinetics of the components of *Augmentin XR* following administration of two *Augmentin XR* tablets at the start of a standardized meal are presented below. —

**Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of Two *Augmentin XR* Tablets (2000/125 mg) to Healthy Adult Volunteers [n=55] Fed a Standardized Meal**

| Parameter (units) | Amoxicillin | Clavulanate |
|---|---|---|
| AUC(0-inf) (µg.h/mL) | 71.6 (16.5) | 5.29 (1.55) |
| $C_{max}$ (µg/mL) | 17.0 (4.0) | 2.05 (0.80) |
| $T_{max}$ (hours)† | 1.50 (1.00-6.00) | 1.03 (0.75-3.00) |
| $T_{1/2}$ (hours) | 1.27 (0.20) | 1.03 (0.17) |
| | | |
| | | |

†median (range)

The half-life of amoxicillin after the oral administration of *Augmentin XR* is approximately 1.3 hours, and that of clavulanate is approximately 1.0 hour.

Clearance of amoxicillin is predominantly renal, with approximately 60% to 80% of the dose being excreted unchanged in urine, whereas clearance of clavulanate has both a renal (30% to 50%) and a non-renal component.

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

In a study in adults, the pharmacokinetics of amoxicillin and clavulanate were not affected by administration of an antacid (Maalox®), either simultaneously with or two hours after *Augmentin XR*.

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

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

## DOSAGE AND ADMINISTRATION

*Augmentin XR* should be taken at the start of a meal to enhance the absorption of amoxicillin and to minimize the potential for gastrointestinal intolerance. Absorption of the amoxicillin component is decreased when *Augmentin XR* is taken on an empty stomach (see Clinical Pharmacology ——— ).

The recommended dose of *Augmentin XR* is 4000 mg/250 mg daily according to the following table:

| Indication | Dose | Duration |
|---|---|---|
| Acute Bacterial Sinusitis | 2 tablets q12h | 10 days |

| | | |
|---|---|---|
| Community Acquired Pneumonia | 2 tablets q12h | 7-10 days |

***Augmentin*** **Tablets (250 mg or 500 mg) CANNOT be used to provide the same dosages as *Augmentin XR*. This is because *Augmentin* XR contains 62.5 mg of clavulanic acid, while the *Augmentin* 250 mg and 500 mg tablets each contain 125 mg of clavulanic acid. In addition, the Extended Release Tablet provides an extended time course of plasma amoxicillin concentrations compared to immediate release Tablets. Thus, two *Augmentin* 500 mg tablets are not equivalent to one *Augmentin XR* tablet.**

**Renally impaired patients:** The pharmacokinetics of *Augmentin XR* have not been studied in patients with renal impairment. *Augmentin XR* is contraindicated in severely impaired patients with a _____ rate of <30 mL/minute and in hemodialysis patients (See CONTRAINDICATIONS _____ ).

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

**Pediatric Use:** Safety and effectiveness in pediatric patients below the age of _____ have not been established.

**Geriatric Use:** No dosage adjustment is required for the elderly (see PRECAUTIONS).

**COMMENTS**

It was observed that the dissolution pattern changed for the 24-month stability batches. Compared with dissolution pattern for initial testing, the release from the sustained release layer for the 24-month stability batches was slower. It is unknown how the changes would affect the *in vivo* absorption / oral bioavailability of amoxicillin.

**RECOMMENDATION:**

The application has been reviewed and found acceptable provided the sponsor agrees with the Agency's recommendation on dissolution specification and labeling changes.

_____

Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT initialed by P. COLANGELO, Pharm.D., Ph.D., Acting Team Leader _____

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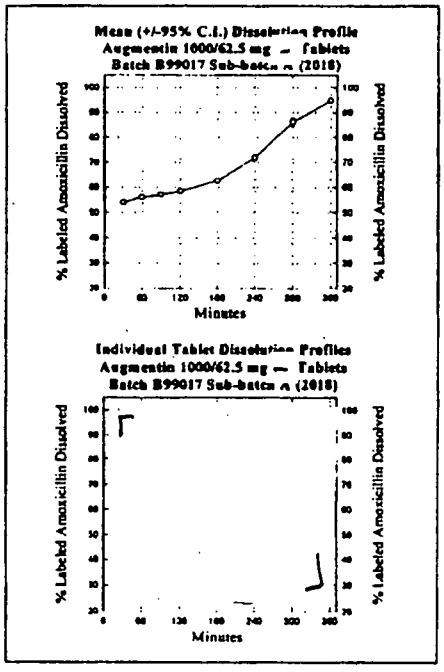
**4.A.2.9 Figure 17 Amoxicillin Dissolution Profile for Augmentin XR™ Tablets, Batch B99017A, 28-count HDPE Bottle at 25°C/60%RH (24 months)**

**Updated**

AUGMENTIN 1000/62.5 mg Tablets
Amoxicillin Dissolution Profile
Batch B99017A, 28-count Bottle (2018)
Stored at 25°C/60% Relative Humidity for 24 Months

| | % Labeled Amoxicillin Dissolved | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Tablet No. | 30 Minutes | 60 Minutes | 90 Minutes | 120 Minutes | 180 Minutes | 240 Minutes | 300 Minutes | 360 Minutes |
| 1 | [redacted] | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | | | | | | | | |
| 10 | | | | | | | | |
| 11 | | | | | | | | |
| 12 | | | | | | | | [redacted] |
| Mean | 54.08 | 56.11 | 57.23 | 58.48 | 62.72 | 71.86 | 86.20 | 94.79 |
| %CV | 1.8 | 1.2 | 1.2 | 1.2 | 2.0 | 2.3 | 3.0 | 0.9 |
| Minimum | [redacted] | | | | | | | [redacted] |
| Maximum | | | | | | | | |

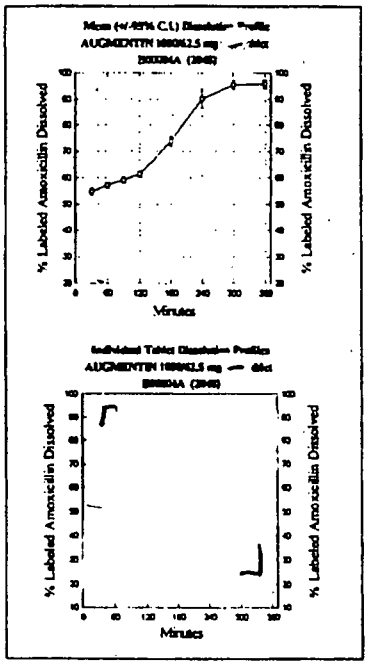


**4.A.2.9 Figure 33 Amoxicillin Dissolution Profile for Augmentin XR™ Tablets, Batch B00004A, 28-count HDPE Bottle at 25°C/60%RH (12 months)**

**Added**

AUGMENTIN 1000/62.5 mg — Tablets
Amoxicillin Dissolution Profile
Batch B00004A, 28-Count HDPE Bottle (2048)
12 month Stability Testing @ 25C/60%RH

| | % Labeled Amoxicillin Dissolved | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Tablet No. | 30 Minutes | 60 Minutes | 90 Minutes | 120 Minutes | 180 Minutes | 240 Minutes | 300 Minutes | 360 Minutes |
| 1 | [redacted] | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | | | | | | | | |
| 10 | | | | | | | | |
| 11 | | | | | | | | |
| 12 | | | | | | | | [redacted] |
| Mean | 54.79 | 57.22 | 59.10 | 61.32 | 73.91 | 90.23 | 95.39 | 95.78 |
| % CV | 2.6 | 1.9 | 1.9 | 1.8 | 2.7 | 3.8 | 1.9 | 1.6 |
| Minimum | [redacted] | | | | | | | |
| Maximum | | | | | | | | |



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/s/

Jenny Zheng
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