CLINICAL PHARMACOLOGY REVIEW

NDA(s): 50-785	Submission Date(s): • 10 Nov 2009 (SDN 126) • 01 Feb 2010 (SDN 130) • 26 Jul 2010 (SDN 132) • 29 Jul 2010 (SDN 133)
Drug	Amoxicillin/Clavulanate Potassium Extended-Release
Trade Name	Augmentin™ XR
OCP Reviewer	Aryun Kim, Pharm.D.
OCP Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP (520)
Sponsor	GlaxoSmithKline
Relevant IND(s)	IND 16,896
Submission Type; Code	**Prior Approval Labeling Supplement, SLR-012** (Pharmacokinetics and dosing for pediatric patients <16 years old & ≥40 kg)
Formulation; Strength(s)	Extended-release tablet provided as a white, oval, film-coated bi-layer scored tablet, containing amoxicillin trihydrate and amoxicillin sodium equivalent to a total of 1,000 mg of amoxicillin and clavulanate potassium equivalent to 62.5 mg of clavulanic acid
Indication	For the treatment of patients of ≥16 years of age with community-acquired pneumonia (CAP) or acute bacterial sinusitis (ABS) due to confirmed, or suspected β-lactamase-producing pathogens and *Streptococcus pneumoniae* with reduced susceptibility to penicillin
Dosage and Administration	CAP: 2 tablets orally every 12 hours for 7-10 days ABS: 2 tablets orally every 12 hours for 10 days

1. Background

On 04 Nov 2008, the Sponsor submitted the final study report for Study AUG102821 (pharmacokinetic study in pediatric patients with suspected acute bacterial sinusitis, <16 years of age, and weighing ≥40 kg) to fulfill the post-marketing commitment for evaluation of AUGMENTIN™ XR in pediatric patients (PMR/PMC-1, SDN 116). See **Clinical Pharmacology Review** of the submitted study report for Study AUG102821, **dated 04 Nov 2009**.

The Sponsor was requested to provide complete analytical data (validation and study-specific results), in order to amend the AUGMENTIN™ XR label with pharmacokinetic results from Study AUG102821. Accordingly, Prior Approval Labeling Supplement, SLR-012, was submitted by the Sponsor on 01 Feb 2010 to update pediatric labeling. Analytical data submissions (10 Nov 2009, SDN 126; 29 Jul 2010, SDN 133) and associated labeling changes (01 Feb 2010, SDN 130; 26 Jul 2010, SDN 132) are discussed herein.

2. Summary of Findings

Plasma concentrations of amoxicillin and clavulanate (components of AUGMENTIN™ XR) in Study AUG102821 were determined by validated protein precipitation and liquid chromatography with tandem mass spectrometry (HPLC/MS-MS). Analytical results are summarized in **Table 2.1**.

Table 2.1 Summary of analytical methods for quantification of amoxicillin and clavulanate

Analyte	**Amoxicillin**	**Clavulanate**	Comments
VALIDATION			
Analytical Report	WD2003-00232	WD2003-00240	
Method	HPLC-MS/MS	HPLC-MS/MS	
Matrix	Plasma	Plasma	
Range	0.05-10 µg/mL	0.05-10 µg/mL	Satisfactory
LLOQ	0.05 µg/mL	0.05 µg/mL	Satisfactory
ULOQ	10 µg/mL	10 µg/mL	Satisfactory
QC samples	0.05, 0.1, 6, 8, 10 µg/mL	0.05, 0.2, 5, 8, 10 µg/mL	Satisfactory
Precision			
Intra-day	≤8.5 %CV	≤12.7 %CV	Satisfactory
Inter-day	≤8.0 %CV	≤10.1 %CV	Satisfactory
Accuracy			
Intra-day	Within ± 13.8%	Within ± 14.6%	Satisfactory
Inter-day	Within ± 5.8%	Within ± 9.4%	Satisfactory
STUDY AUG102821			
Analytical Report	WD2007-01331	WD2007-01000	
Method	HPLC-MS/MS	HPLC-MS/MS	
Matrix	Plasma	Plasma	
Range	0.05-10 µg/mL	0.05-10 µg/mL	Satisfactory *(Dilution factor 10 with 20 µg/mL for amoxicillin & clavulanate)*
LLOQ	0.05 µg/mL	0.05 µg/mL	Satisfactory
ULOQ	10 µg/mL	10 µg/mL	Satisfactory *(Dilution factor 10 with 20 µg/mL for amoxicillin & clavulanate)*
Linearity	≥0.9961	≥0.991	Satisfactory
QC samples	0.1, 6, 8 µg/mL	0.2, 5, 8 µg/mL	Satisfactory
Precision			
Intra-day	≤12.1 %CV	≤18.6 %CV	Satisfactory *(67% of samples within ± 15% of nominal value for clavulanate)*
Inter-day	≤6.3 %CV	≤16.2 %CV	Satisfactory *(67% of samples within ± 15% of nominal value for clavulanate)*
Accuracy			
Intra-day	Within ± 14.9%	Within ± 46.0%	Satisfactory *(67% of samples within ± 15% of nominal value for clavulanate)*
Inter-day	Within ± 3.3%	Within ± 3.7%	Satisfactory
Stability			
At -80 ºC	5 months	9 months	Satisfactory
Study Date	19 Jan 2006 - 2 Apr 2007	19 Jan 2006 - 2 Apr 2007	Satisfactory
Analysis Date	16 Mar 2006 - 19 Apr 2007	23 Mar 2006 - 8 May 2007	Satisfactory

LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

3. Recommendation

Submitted analytical results for Study AUG102821 are acceptable. AUGMENTIN™ XR label should be revised to include pediatric pharmacokinetic results, as indicated below.

Revisions made by the Reviewer (in conjunction with the Medical Officer and subsequent concurrence by the Sponsor with minor edits from 29 Jul 2010) to the Sponsor's proposed labeling (draft version 01 Feb 2010) are indicated in blue underlined font for inserted text and in ~~red strikethrough font~~ for deleted text. Affected sections were **CLINICAL PHARMACOLOGY**; **PRECAUTIONS, Pediatric Use**; and **DOSAGE AND ADMINISTRATION, Pediatric Use**.

CLINICAL PHARMACOLOGY

In a study of (b) (4) pediatric patients with acute bacterial sinusitis~~-~~ (b) (4) , 7 to 15 years of age, and weighing at least 40 kg~~)~~, the pharmacokinetics of amoxicillin and clavulanate were assessed following administration of AUGMENTIN XR 2000 mg/125 mg (as two 1000 mg/62.5 mg tablets) (b) (4) every 12 hours with food (Table 2).

Table 2. Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of Two AUGMENTIN XR Tablets (2,000 mg/125 mg) Every 12 Hours With Food to (b) (4) -Pediatric Patients (7 to 15 Years of Age and Weighing ≥40 kg) With Acute Bacterial Sinusitis

Parameter (units)	Amoxicillin (n=24)	Clavulanate (n=23)
$AUC_{(0-\tau)}$ (mcg•hr/mL)	(b) (4) 57.8 (15.6)	(b) (4) 3.18 (1.37)
C_{max} (mcg/mL)	11.0 (3.34)	1.17 (0.67)
T_{max} (hours)[a]	2.0 (1.0 – 5.0)	2.0 (1.0 – 4.0)
$T_{½}$ (hours)	(b) (4) 3.32 (2.21)[b]	(b) (4) 0.94 (0.13)[c]

[a] Median (range).

[b] n=18.

[c] n=17.

PRECAUTIONS

Pediatric Use: (b) (4) The safety and effectiveness of AUGMENTIN XR have been established for pediatric patients weighing ≥40 kg who are able to swallow tablets. Use of AUGMENTIN XR in these pediatric patients is supported by evidence from adequate and well-controlled trials of adults with acute bacterial sinusitis and community-acquired pneumonia with additional data from a pediatric pharmacokinetic study.

A pharmacokinetic study in (b) (4) -pediatric patients (7 to 15 years of age and weighing ≥40 kg) (b) (4) -was conducted (see CLINICAL PHARMACOLOGY). The adverse event profile in (b) (4) 44 patients who received at least one dose of AUGMENTIN XR was consistent with the established adverse event profile for the product in adults.

DOSAGE AND ADMINISTRATION

Pediatric Use: (b) (4) Pediatric patients who weigh 40 kg or more and can swallow tablets should receive the adult dose.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50785	PMR/PMC-1	GLAXOSMITHKLINE	AUGMENTIN XR(AMOXICILLIN/CLAVULANATE POT
NDA-50785	SUPPL-12	GLAXOSMITHKLINE	AUGMENTIN XR(AMOXICILLIN/CLAVULANATE POT

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/s/

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08/24/2010

CHARLES R BONAPACE
08/24/2010