

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50761

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

NDA 50,760
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Amoxil Chewable Tablet and Suspension

DATE of SUBMISSION
April 15, 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

SPONSOR: SmithKline Beecham
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101

REVIEWER: HE SUN, Ph.D.

I. BACKGROUND

The sponsor submitted these NDAs to support Amoxil (amoxicillin) chewable tablet and suspension formulations, to allow for the change in the dosing regimen of amoxicillin from thrice daily to twice daily dosing in pediatric patients, and to provide support for the new formulations. These new Amoxil formulations (200 mg and 400 mg in strength) are matched to Augmentin (amoxicillin/clavulanate potassium) chewable tablet and suspension antibiotic containing amoxicillin that was approved on May 31, 1996 for twice daily dosing.

A three-way, cross-over bioequivalence study in 24 evaluable healthy adult volunteers (male and female) comparing the new 400-mg Amoxil chewable tablet and suspension formulations to the marketed *Augmentin* suspension formulation is the only study included in the submission.

II. STUDY SUMMARY

Study # BRL-002333

Study Type: Bioequivalence

Study Title: A study to determine the bioequivalence of amoxicillin in novel chewable tablet (400mg) and suspension formulation (400mg/5ml) of Amoxil to the marketed suspension formulation of Augmentin (contains 400mg amoxicillin/5ml).

Investigator:

Study design and execution:

Objective	To demonstrate the BE of amoxicillin in a novel chewable tablet (400mg) and a novel suspension formulation (400mg/5ml) of Amoxil to the standard marketed suspension formulation of augmentin (400mg amoxicillin/5ml).
Design Dosage Dosing method	Randomized, open label, single dose 3-way crossover design. 400 mg chewable tablet and 400mg/5ml suspension of Amoxil. 400mg Amoxicillin/5ml Augmentin. Each subject receives three single doses of each of the formulations. At least 3 days of washout time.
Subject Category Gender Age	Total of 27 male and female subjects were included, 24 were evaluable. Normal healthy volunteers Male and female Adults, 18 to 60 years old.
Assay	Acceptable.
PK analysis	AUC _t , AUC _{inf} , C _{max} , T _{max} and t _{1/2}

Results:

TABLE 1. MEAN (SD) PHARMACOKINETIC PARAMETERS FOR AMOXICILLIN (N=24)

Parameters	Amoxil Chewable Tablet	Amoxil Suspension	Augmentin Suspension
AUC _{inf} (ug.hr/ml)	17.9(2.4)	17.1(3.1)	18.0(3.1)
AUC _{0-t} (ug/hr/ml)	17.6(2.4)	16.9(3.1)	17.9(3.2)
C _{max} (ug/ml)	5.18(1.64)	5.92(1.62)	5.61(1.53)
T _{1/2}	1.29(0.34)	1.29(0.24)	1.26(0.21)
T _{max} (hours)	1.50(0.5-4.0)	1.00(1.0-4.02)	1.26(0.52-3.0)

TABLE 2. POINT ESTIMATE AND 90% CI (N=24) FOR COMPARING THE NEW FORMULATIONS TO AUGMENTIN

Parameters	Comparison ¹	Point Estimate	90% CI
AUC _{inf}	A:C	1.01	0.94-1.08
	B:C	0.95	0.89-1.02
AUC _{0-t}	A:C	0.99	0.92-1.06
	B:C	0.94	0.88-1.01
C _{max}	A:C	0.92	0.82-1.02
	B:C	1.05	0.95-1.17
T _{1/2}	A-C	0.03	
	B-C	0.02	
T _{max}	A-C	-0.01	
	B-C	-0.25	

1. A: Chewable tablet, B: Suspension, C: Augmentin suspension

TABLE 3. POINT ESTIMATE AND 90% CI FOR COMPARING THE NEW CHEWABLE TABLET AND SUSPENSION FORMULATION.

Parameters	Comparison ¹	Point Estimate	90% CI
AUC _{inf}	A:B	1.06	0.98-1.13
AUC ₀₋₄	A:B	1.05	0.98-1.13
C _{max}	A:B	0.87	0.78-0.97
T _{1/2}	A-B	0.00	
T _{max}	A-B	0.25	

1. A: Chewable tablet, B: Suspension

Conclusion and discussion:

Both the novel chewable tablet and the suspension formulation of Amoxil (400mg) can be considered bioequivalent to amoxicillin component of the standard marketed formulation of Augmentin (400/57mg/5ml).

Bioequivalence was not fully demonstrated for the novel chewable tablet relative to the suspension formulation of Amoxil. Confidence intervals for AUC were within the acceptance range, but the lower end of the 90% CI for C_{max} fell below the BE bound by 2%.

III. DISSOLUTION STUDY

The dissolution testing method used for chewable tablet to generate the dissolution data was not included in the original NDA submission. The information was found in the Chemistry Section of the NDA and some other information was faxed FDA on Dec. 10, 1998.

Method: Using USP apparatus 2 (rotation paddle), at 75 rpm, with 900 ml deionized water at 37°C±0.5°C. Results are listed in attachment.

Based on the data, the proposed specification is: For Amoxil 200 mg and 400 mg chewable tablets, Q₁₀ % of labeled amoxicillin dissolved in 10 min.)

The dissolution test for suspension was submitted on Jan. 13, 1999. Two bottles from one batch (100mg presentations) of suspension of each strength were taken from storage at 4C (23 months storage). The bottles were individually reconstituted and pooled for each strength. Six 10ml samples were obtained on each strength. Amoxicillin concentrations were analyzed by

Results show that for the 200 and 400 mg strength product 100 % of amoxicillin is dissolved at 10 minutes. The dissolution of amoxicillin in the 400-mg strength product slightly lower than that of 200mg strength at 10 minutes.

IV. RECOMMENDATION

1. The BE study shows that bioavailabilities of amoxicillin from the new Amoxil chewable tablet and suspension formulation are equivalent to that from marketed Augmentin suspension formulation.

2. From a biopharmaceutics standpoint, failure to demonstrate bioequivalence between the chewable tablet and the suspension formulations is not unexpected generally. The study is acceptable since both newer to be marketed products are bioequivalent to an approved Augmentin suspension.
3. The to be marketed Amoxil 200 and 400 mg chewable and suspension formulations are new formulations, according to general rule, at least one food effect study is required for each formulation. This comment was sent to the sponsor at the time of filing. However, no report was received yet. Accordingly, "The effect of food on the absorption of amoxicillin from Amoxil tablets has not been investigated" language should be incorporated in the drug label.
4. The 200-mg and 400-mg suspension formulations are similar in formulation ingredients. The 200-mg and 400-mg chewable tablet formulations are proportional in formulation ingredients. Therefore, in vivo study of the low strength formulations, 200mg chewable tablet and suspension, can be waived.
5. Dissolution studies for the chewable tablets were found in the Chemistry Section of the NDA and other information was faxed on Dec. 10, 1998 upon request. Based on data received, the reviewer recommends that the dissolution specification for Amoxil 200 mg and 400 mg chewable tablets to be modified to: Q % of labeled amoxicillin dissolved in min.
6. Dissolution data for suspension formulations (200 and 400 mg) shows total dissolution for both strength are % at minutes although the 400 mg strength dissolves a little slower at 10 minutes. Study is acceptable.
7. Labeling comments are marked on the annotated labeling and was forward to the review team.

IS

11/26/99

// He Sun, Ph.D.

Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D.

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1/26/99

Optional Intra-Divisional CPBB Dec. 15, 1998

cc:

NDA 50,760; 50,761

HFD-520 (Clinical, CSO)

HFD-340 (Viswanathan)

HFD-880 (Pelsor, Sun)

HFD-880 Div. File NDA 50,760, 50,761 (Amoxicillin)