CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

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<th>DATE RECEIVED:</th>
<th>July 31, 2001</th>
<th>DUE DATE:</th>
<th>August 24, 2001</th>
<th>OPDRA CONSULT #:</th>
<th>01-0076-1</th>
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TO: Janice Soreth, MD
Acting Director, Division of Anti-Infective Drug Products
HFD-520

THROUGH: Susmita Samanta, Project Manager
HFD-520

PRODUCT NAME: Augmentin XR
(amoxicillin/clavulanate potassium extended-release tablets)
1000 mg/62.5 mg

NDA #: 50-785

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Anti-Infective Drug Products (HFD-520), OPDRA conducted a review to evaluate the appropriateness of the modifier “XR” with the proprietary name “Augmentin” to determine the potential for confusion with approved proprietary names and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not object to the use of the proposed modifier “XR” with the approved proprietary name “Augmentin”, if the Division agrees that this is truly an extended-release tablet.

APPEARS THIS WAY ON ORIGINAL

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration
Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B32  
Center for Drug Evaluation and Research  

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** August 17, 2001  
**NDA NUMBER:** 50-785  
**NAME OF DRUG:** Augmentin XR  
(amoxicillin/clavulanate potassium extended-release tablets)  
1000 mg/62.5 mg  
**NDA HOLDER:** GlaxoSmithKline

I. **INTRODUCTION**

This consult was written in response to a secondary request from the Division of Anti-Infective Drug Products (HFD-520) regarding the proposed modifier “XR” with the approved proprietary name “Augmentin” to determine the potential for confusion with approved proprietary names and generic names as well as pending names.

OPDRA initially reviewed the proprietary name “Augmentin ES” on May 17, 2000 for the 600 mg/5 mL (600 mg of amoxicillin and 42.9 mg of clavulanate potassium) application under NDA 50-755. The ratio of amoxicillin to clavulanate potassium is 14:1. OPDRA did not recommend the modifier “ES” to the Augmentin name for the new strength. The modifier “ES” implies extra strength and this could be misleading, since Augmentin 875 tablet is currently available. OPDRA recommended the proprietary name Augmentin 600, which is consistent with the existing nomenclature and naming for the oral solutions (Augmentin 125, Augmentin 200, Augmentin 250, and Augmentin 400).

Following a July 19, 2000 meeting with the sponsor, the division decided to accept the name Augmentin ES since there was no safety issue. In addition, the sponsor reported that

On December 20, 2000 the Sponsor submitted NDA 50-785 for a higher strength of Augmentin extended-release tablets which contain 1000 mg of amoxicillin and 62.5 mg of clavulanate potassium. The ratio of amoxicillin to clavulanate potassium is 16:1. The sponsor requested the use of the proprietary name “Augmentin” for this new strength
However, on June 18, 2001 the sponsor withdrew the Augmentin name from the tablet product.

II. SAFETY EVALUATOR RISK ASSESSMENT

"XR" is a common modifier used to express an extended-release formulation. There are many approved extended-release drug products with proprietary names that contain the modifier "XR" such as Tegretol XR, Voltaren XR, Dilacor XR, Glucophage XR, and Effexor XR. Therefore, OPDRA has no objections to the use of the modifier "XR" with the approved proprietary name "Augmentin" for the 1000 mg extended-release tablet formulation. This is contingent on the fact that this drug product is truly an extended-release formulation.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft container label, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified the following areas of possible improvement, in the interest of minimizing potential user error.

- **Container Label**

1. When reviewing a comparison of the various Augmentin labels, we observe that the expression of strength (1000 mg) is less prominent. We would recommend increasing the prominence to be similar to the other strengths.

2. We see no reason to state that We find this quite distracting and recommend it be deleted. This would be consistent with the 20 tablet package sizes of 500 mg and 875 mg (both 10 day course of treatment).
IV. RECOMMENDATIONS

A. OPDRA has no objections to the use of the modifier “XR” with the approved proprietary name “Augmentin”; if the Division agrees that this is truly an extended-release tablet.

B. OPDRA has recommended labeling interventions that might minimize user error.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-----------------
Alina Mahmud
8/22/01 11:29:28 AM
PHARMACIST

Jerry Phillips
8/22/01 12:57:25 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL
FACSIMILE TRANSMISSION

DATE: 12-13-01  Number of Pages(including cover sheet): 5

TO: Mr. Ed Yuhao

COMPANY: Mayo Smith Kline

FAX NUMBER: 215-751-4926

MESSAGE: Faxing Action Letter for NDA 50-785, Augmentin XR

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Susmitha Samanta

TITLE: Regulatory Project Manager

TELEPHONE: 301-827-2125  FAX NUMBER: 301-827-2327/2325

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Thank you.
WITHHOLD 104 PAGE (S)

Draft Labeling
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS
   SmithKline Beecham Pharmaceuticals  
   One Franklin Plaza  
   P.O. Box 7929  
   Philadelphia, PA 19101-7929

2. TELEPHONE NUMBER (Include Area Code)
   (215) 751-3468

3. PRODUCT NAME
   Augmentin

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  
   IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE  
   AND SIGN THIS FORM.  
   IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:
   ☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.  
   ☑ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY  
     REFERENCE TO  
     (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER
   4064

6. LICENSE NUMBER / NDA NUMBER
   N0507785

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.
   ☑ A LARGE VOLUME PARENTERAL DRUG PRODUCT  
     APPROVED UNDER SECTION 505 OF THE FEDERAL  
     FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/82  
     (Self-Explanatory)
   ☑ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE  
     *(See item 7, reverse side before checking box.)*
   ☑ THE APPLICATION QUALIFIES FOR THE ORPHAN  
     EXCEPTION UNDER SECTION 736(a)(1)(B) OF THE FEDERAL FOOD,  
     DRUG, AND COSMETIC ACT  
     *(See item 7, reverse side before checking box.)*
   ☑ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT  
     QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(B) OF  
     THE FEDERAL FOOD, DRUG, AND COSMETIC ACT  
     *(See item 7, reverse side before checking box.)*
   ☑ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL  
     GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED  
     COMMERCIALY (Self-Explanatory)
   ☑ WHOLE BLOOD OR BLOOD COMPONENT FOR  
     TRANSFUSION
   ☑ AN APPLICATION FOR A BIOLOGICAL PRODUCT  
     FOR FURTHER MANUFACTURING USE ONLY
   ☑ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT  
     LICENSED UNDER SECTION 381 OF THE PHS ACT
   ☑ BOVINE BLOOD PRODUCT FOR TOPICAL  
     APPLICATION LICENSED BEFORE 9/1/82

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☑ YES ☑ NO  
   *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0297)  
Hubert H. Humphrey Building, Room 331-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to the address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Associate Director  
U.S. Regulatory Affairs

DATE 12/11/2000
Augmentin (amoxicillin/clavulanate)

BRL-025000

Item 16. Debarment Certification
Item 16. Debarment Certification

Pursuant to section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.
TO: Deneen Stewart  
US Regulatory Affairs  

FROM: Dara L. Dinner  
Associate Patent Counsel  
SB Corporate IP - US  

DATE: 6 December 2000  

RE: Patent Information Respecting Augmentin — New Drug Application (# 50-758) for Management of Specific Bacterial Infections  

Please find below the patent information that SB is required to submit to the U.S. FDA under the provisions of 21 C.F.R. § 314.53 for the "Description" and "How Supplied" sections of the labeling.*  

The composition for which approval is being sought is a formulation having an approximate ratio of 16:1 of amoxicillin and potassium clavulanate in a bilayer tablet dosage form. The immediate release layer of the bilayer tablet contains approximately __________________________  

____________________________; and in the sustained release layer there is approximately __________________________. Thus, each tablet provides a total of 1000 mg amoxicillin and 62.5 mg clavulanic acid (16:1 ratio).
Patent Information for NDA Filings (7 Patents)

Patent 1: U.S. Patent No. 6,031,093\(^1\)

a. Expiration Date
The 17 year term expires on 28 February 2017.

b. Type of Patent
This patent claims:

1) a solid pharmaceutically acceptable salt of clavulanic acid
which is a component of the formulation for which approval is being sought.

c. Name of Patent Owner
SmithKline Beecham p.l.c.

Patent 2: U.S. Patent Number 6,048,977

a. Expiration Date
The 17 year term expires on 28 February 2017.

b. Type of Patent
This patent claims:

1) potassium salt of clavulanic acid which is a component of
the formulation for which approval is being sought.

c. Name of Patent Owner
SmithKline Beecham p.l.c.

\(^1\) FDA recently issued a proposed rule entitled "Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs" (65 Fed. Reg. 3623, Jan. 24, 2000) which the agency attempted to bring its regulations into conformance with certain transitional provisions of the Food and Drug Administration Modernization Act (Section 125 (d) of FDAMA (1997)). In this proposed rule, FDA would exempt marketing applications for certain antibiotic drug products from regulatory provisions governing exclusivity and patents based on a comparison of active moieties. SB disagrees with this proposed rule because it does not reflect Congress's intent for repealing Section 507 of the FD&C Act. SB intends to provide comments to the docket expressing our disagreement with this proposed rule and believes the rule should be changed to reflect these comments. SB was required to perform clinical studies on Augmentin \(\rightarrow\) to show that it is safe and effective for its intended use. Therefore, the product should receive three years exclusivity under the Hatch-Waxman Act, which is the same period that is available to non-antibiotic drugs
**Patent 3:**  
**U.S. Patent Number 6,051,703**

a. Expiration Date

The 17 year term expires on 28 February 2017.

b. Type of Patent

This patent claims:

1) a purified pharmaceutically acceptable salt of clavulanic acid which is a component of the formulation for which approval is being sought.

2) a purified solid pharmaceutically acceptable salt of clavulanic acid which is a component of the formulation for which approval is being sought.

3) purified clavulanic acid or a pharmaceutically acceptable salt thereof, which is a component of the formulation for which approval is being sought.

c. Name of Patent Owner

SmithKline Beecham p.l.c.

**Patent 4:**  
**U.S. Patent Number 4,529,720**

a. Expiration Date

The 17 year term expires on July 16, 2002.

b. Type of Patent

This patent claims:

1) generically, a method of effecting β-lactamase inhibition in a human [with β-lactamase producing bacteria] with clavulanic acid or a pharmaceutically acceptable salt thereof, which claims contain a component of the formulation for which approval is being sought.

2) specifically claims the administration of the potassium salt of clavulanic acid, and also oral administration of clavulanic acid or salt thereof, and purely synthetic antibiotic drugs. For this reason, we are submitting the patent information on *Augmentin* to receive three years exclusivity and to be listed in The Orange Book.
which claims cover a component of the formulation for which approval is being sought.

- Name of Patent Owner
  Beecham Group, p.l.c.

**Patent 5: U.S. Patent Number 4,560,552**

a. Expiration Date
   The 17 year term expires on December 24, 2002.

b. Type of Patent
   This patent claims:
   1) a generic pharmaceutical composition for treating bacterial infections in a human with a synergistically effective amount of clavulanic acid, or a pharmaceutically acceptable salt thereof, and an antibacterially effective amount of a penicillin, or a pharmaceutically acceptable salt or ester thereof, which claims cover the both active ingredients in the formulation for which approval is being sought.

c. Name of Patent Owner
   Beecham Group p.l.c.

**Patent 6: U.S. Patent Number 4,525,352**

a. Expiration Date
   The 17 year term expires on June 25, 2002

b. Type of Patent
   This patent claims:
   1) a generic pharmaceutical composition for treating bacterial infections in a human with a synergistically effective amount of a pharmaceutically acceptable salt of clavulanic acid, and an antibacterially effective amount of amoxicillin, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof, in combination
with a pharmaceutically acceptable carrier, which claims cover both of the active ingredients in the formulation for which approval is being sought.

2) specifically claims the potassium salt of clavulanic acid, as a component of the formulation for which approval is being sought.

3) specifically claims the trihydrate form of amoxicillin, as a component of the formulation for which approval is being sought.

4) a generic method of treating bacterial infections in humans with a synergistically effective amount of a pharmaceutically acceptable salt of clavulanic acid, and an antibacterially effective amount of amoxicillin, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof, in combination with a pharmaceutically acceptable carrier, which claims a use for which approval is being sought.

5) specifically claims the potassium salt of clavulanic acid and amoxicillin trihydrate, which claims cover use of both active agents in the formulation for which approval is being sought.

c. Name of Patent Owner
   Beecham Group p.l.c.

Patent 7: U.S. Patent Number 4,454,069

a. Expiration Date
   The 17 year term expires on June 12, 2001.

b. Type of Patent
   This patent claims:
   1) a method for the production of clavulanic acid, or a pharmaceutically acceptable salt thereof, which claims cover production of a component of the formulation for which approval is being sought.

c. Name of Patent Owner
   Beecham Group Limited
New drug applications under section 505(b) for drugs that contain "old" antibiotics are not eligible for exclusivity under sections 505(c)
Augmentin (amoxicillin/clavulanate)

BRL-025000

Item 15. Establishment Description

Sharon Maglennon*

*USRA

SB Document Number: BRL-025000/RSD-101GNX/1

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<td>Sharon Maglennon Assistant Director</td>
<td>tel: 610-917-6457</td>
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Shewalton Road  
Irvine KA11 SAP  
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Assistant Director  
Regulatory Affairs – North America  
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United Kingdom  
Currently approved under DMF | Sharon Maglennon  
Assistant Director  
Regulatory Affairs – North America  
SmithKline Beecham Pharmaceuticals | tel: 610-917-6457  
fax: 610-917-4104 | CFN No. FCUK 691 | 12/20/00 |
### ACTIVE INGREDIENT (AMOXICILLIN SODIUM)

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<td>Manufacturing, Release and Stability Testing</td>
<td>SmithKline Beecham Pharmaceuticals</td>
<td>Linda Schipmann Quality Assurance Manager</td>
<td>tel: 732-469-5200 ext. 4309</td>
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<td>101 Possumtown Road</td>
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<td>SmithKline Beecham Pharmaceuticals 201 Industrial Drive Bristol, TN 37620</td>
<td>Sharon Maglenon Assistant Director Regulatory Affairs – North America SmithKline Beecham Pharmaceuticals</td>
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Team Leader Memorandum
NDA 50-785 Augmentin® XR Extended Release Tablets

Applicant: GlaxoSmithKline
Product Name: Augmentin® XR
Active Ingredients: Amoxicillin and Clavulanic Acid
Formulation: Extended release tablets containing 1000 mg of amoxicillin and 62.5 mg of clavulanate

Submission Date: March 29, 2002
Memorandum Date: September 27, 2002

Augmentin® XR is a new formulation of a combination product containing amoxicillin and clavulanate in a 16:1 ratio. Augmentin XR tablets contain 1000 mg of amoxicillin and 62.5 mg of clavulanate. The recommended dose regimen, two tablets every 12 hours for 7-10 days, provides the same daily dose of clavulanate (250 mg/day) as the previously approved 7:1 formulation. However, the daily dose of amoxicillin is more than doubled (4000 mg/day for Augmentin XR compared to 1750 mg/day for the 7:1 tablets). In addition, Augmentin XR has extended release characteristics that maintain higher serum concentrations of amoxicillin over a longer portion of the dosing period.

Augmentin® XR was specifically developed to provide sustained amoxicillin concentrations for treatment of penicillin-resistant Streptococcus pneumoniae (PRSP). In pharmacokinetic studies of healthy volunteers, the mean time (expressed as a proportion of the 12-hour dose interval) above a minimum inhibitory concentration (T>MIC) of 4 µg/mL for this product was 49%. There is support in the literature for the concept that T>MIC for amoxicillin correlates with effectiveness against Streptococcus pneumoniae in animal models of infection. These results were used by the applicant to support moving into phase 3 trials with this formulation. During review of this application, an important limitation was noted with regard to this pharmacodynamic information. There is a great deal of variability in the serum concentrations of amoxicillin. As a result, roughly 10% (9/55) volunteers had a T>MIC ≤ 32%. Therefore, a proportion of the patient population treated with Augmentin® XR may not achieve adequate T>MIC for Streptococcus pneumoniae with an MIC of 4 µg/mL. This leads to the concern that a proportion of infections due to PRSP with an MIC ≥ 4 µg/mL would not be adequately treated with Augmentin® XR.

Several phase 3 trials of patients with community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) were conducted by the applicant. These studies included both blinded, comparator-controlled studies and open-label non-comparative trials. The latter were large studies performed to accumulate clinical data on the use of Augmentin® XR for the treatment of PRSP infections.

In CAP, a controlled study (#546) compared Augmentin® XR with the Augmentin® (7:1) formulation already marketed in the U.S. In this study, clinical success rates at the test of cure visit for the per protocol population were 86.3% for Augmentin® XR and 91.2% for
the Augmentin® 7:1 formulation with a 95% confidence interval for the treatment difference of (-11.0, 1.2). In the intent-to-treat (ITT) population, these rates were 78.0% for Augmentin® XR and 82.6% for the Augmentin® 7:1 formulation with a 95% confidence interval for the treatment difference of (-11.4, 2.3). Similar results were reported in a comparative study (#556) that used a European formulation of Augmentin® (not FDA approved).

The following table summarizes the clinical outcomes in the CAP patients with PRSP treated with Augmentin® XR. When categorized by penicillin MIC, the limited experience in CAP patients with S. pneumoniae with a penicillin MIC of 4 µg/mL is apparent. The experience for CAP patients with S. pneumoniae isolates with a penicillin MIC of 2 µg/mL is greater. The cure rate and 95% confidence interval are similar to those for penicillin-susceptible S. pneumoniae.

<table>
<thead>
<tr>
<th>Penicillin MIC of S. pneumoniae Isolates</th>
<th>Intent To Treat</th>
<th>Clinically Evaluable</th>
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<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>All S. pneumoniae</td>
<td>184/214</td>
<td>86.0</td>
</tr>
<tr>
<td>MIC ≥2.0 µg/ml</td>
<td>17/20</td>
<td>85.0</td>
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<tr>
<td>MIC = 2.0 µg/ml</td>
<td>13/14</td>
<td>92.9</td>
</tr>
<tr>
<td>MIC = 4.0 µg/ml</td>
<td>4/6</td>
<td>66.7</td>
</tr>
</tbody>
</table>

Overall, these results provide substantial evidence for the effectiveness of Augmentin® XR in the treatment of CAP. The experience with PRSP isolates support the activity of Augmentin® XR for the treatment of CAP patients with PRSP isolates that have a penicillin MIC of 2 µg/mL. It should be noted that the controlled studies did not demonstrate a particular advantage to the use of Augmentin® XR over approved formulations of Augmentin®. For patients that do not have PRSP, the Augmentin® 7:1 formulation provides similar effectiveness with less drug. Augmentin XR should be reserved for the treatment CAP patients at risk for PRSP.

For ABS, a controlled study (#550) compared Augmentin® XR with levofloxacin 500 mg/day. In this study, clinical success rates at the test of cure visit for the per protocol population were 83.7% for Augmentin® XR and 84.3% for levofloxacin with a 95% confidence interval of (-9.4, 8.3). In the ITT population, these rates were 76.4% for Augmentin® XR and 83.0% for levofloxacin with a 95% confidence interval for the treatment difference of (-14.9, 1.7).

The table on the following page summarizes the outcomes for ABS patients with PRSP. As with the CAP experience, there is greater experience in ABS patients with S. pneumoniae isolates with a penicillin MIC of 2 µg/mL. The point estimate of the cure rate and the 95% confidence interval for these patients are similar to the results for penicillin-susceptible S. pneumoniae. The experience with treatment of CAP due to PRSP with a penicillin MIC of 2 µg/mL also lends support to its activity in ABS. Again, there is limited experience with S. pneumoniae isolates with a penicillin MIC of 4 µg/mL.
Overall, these results provide substantial evidence for the effectiveness of Augmentin® XR in the treatment of ABS. The experience with PRSP isolates supports the activity of Augmentin® XR for the treatment of ABS patients with PRSP isolates that have a penicillin MIC of 2 µg/mL. For patients with PRSP isolates with higher MIC's, the results look promising, but there are several limitations to the data. There is a higher placebo cure rate for ABS. The 95% confidence interval for ABS patients with PRSP with a penicillin MIC of 4 µg/mL is too wide to conclude that Augmentin® XR is more effective than a placebo. Also, there is inadequate evidence of effectiveness for higher MIC isolates in a more serious disease (i.e., CAP) and there are concerns about the variable pharmacokinetics of Augmentin® XR. At this time, the FDA cannot conclude that substantial evidence of effectiveness for treatment of PRSP isolates with penicillin MIC’s of 4 µg/mL or higher for either CAP or ABS. The sponsor has been encouraged to gather more clinical data on treatment of PRSP with penicillin MIC’s of 4 µg/mL.

A total of 4144 patients received Augmentin® XR in phase 3 clinical studies. Of these, 2787 patients received Augmentin® XR in non-comparative studies. In comparative trials, 1357 patients received Augmentin® XR and 1387 received comparator drugs. Adverse events (AE) were reported in 52.3% of Augmentin® XR and 51.3% of comparator patients in the comparative trials. The AE rates for Augmentin® XR were lower in the non-comparative trials, so that 1952/4144 (47.1%) of Augmentin® XR patients in phase 3 trials reported AE. The most common AE in Augmentin® XR patients were diarrhea (17.4%), headache (3.8%), nausea (3.3%), abdominal pain (2.5%), and genital moniliasis (2.2%). Overall, the types of AE for Augmentin® XR are similar to those described for FDA approved formulations of Augmentin®. In one CAP trial, there was a direct comparison of Augmentin® XR (255 patients) with the approved Augmentin® 7:1 formulation (259 patients). The overall rates of adverse events were similar (49.4% vs. 51.4%, respectively) in the two treatment arms. The most common AE was diarrhea (18.0% vs. 14.3%, respectively), but the difference was not statistically significant. Still, higher amounts of amoxicillin in Augmentin® XR are expected to result in higher rates of adverse events for any dose-related AE. Diarrhea was reported in 19.8% of Augmentin® XR patients and 9.9% of comparator patients in the comparative trials.

Overall, the applicant has provided substantial evidence of the safety and effectiveness of Augmentin® XR.
Team Leader Memo for Augmentin XR resubmission; Please sign off.

Janice Soreth  
10/21/02 05:17:45 PM  
MEDICAL OFFICER
PEDIATRIC PAGE
(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 50-785          Supplement Type (e.g. SE5): NA          Supplement Number: NA

mp Date: 3/29/02       Action Date: ______________________

HFD-520 Trade and generic names/dosage form: Augmentin XR™(amoxicillin/clavulanate potassium)
1000/62.5mg Tablet

Applicant: GlaxoSmithKline Therapeutic Class: 3S

Indication(s) previously approved: NA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Community-Acquired Pneumonia

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☐ No: Please check all that apply:  ☑ Partial Waiver  ☑ Deferred  ☑ Completed

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: __________________________

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _kg_  mo. 0  yr. _ Tanner Stage_
Max _kg_  mo. 3  yr. _ Tanner Stage_

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:  _Children between the 0-3 months with this condition are usually treated with IV antibiotics_
If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ______ kg ______ mo. ______ yr. ______ Tanner Stage ______
Max ______ kg ______ mo. ______ yr. 16 Tanner Stage ______

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☒ Adult studies ready for approval

Other: __________________________________________

Date studies are due (mm/dd/yy): 09/25/04

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ______ kg ______ mo. ______ yr. ______ Tanner Stage ______
Max ______ kg ______ mo. ______ yr. ______ Tanner Stage ______

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

[See appended electronic signature page]

Regulatory Project Manager

cc: NDA
    HFD-950/Terrie Crescenzi
    HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337
Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Acute Bacterial Sinusitis

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☒ No: Please check all that apply: ☒ Partial Waiver ☒ Deferred ✗ Completed

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☒ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.
Section C: Deferred Studies

Age/weight range being deferred:

Min ___ kg ___ mo. ___ yr. ___ Tanner Stage ___
Max ___ kg ___ mo. ___ yr. ___ Tanner Stage ___

Reason(s) for deferral:
☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☒ Adult studies ready for approval
☐ Other: ________________________________

Date studies are due (mm/dd/yy): 09/25/02

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ___ kg ___ mo. ___ yr. ___ Tanner Stage ___
Max ___ kg ___ mo. ___ yr. ___ Tanner Stage ___

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: ____________________________

(See appended electronic signature page)

Regulatory Project Manager

cc: NDA
    HFD-960/ Terrie Crescenzi
    (revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Alexander
10/4/02 01:18:24 PM

APPEARS THIS WAY
ON ORIGINAL