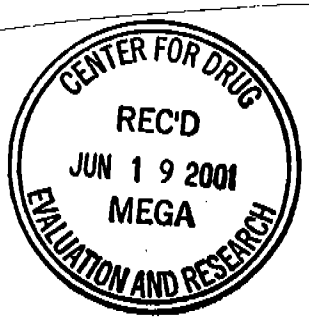
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-755

CORRESPONDENCE

SUPPL NEW CORRESP NC



June 18, 2001

GlaxoSmithKline

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NDA 50-755
Augmentin ES™ (amoxicillin/clavulanate potassium)
Powder for Oral Suspension

Janice Soreth, M.D.
Acting Director, Division of Anti-Infective Drug Products (HFD-520)
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: **Response to FDA Request for Information on Proposed Proprietary Name**

Dear Dr. Soreth:

Reference is made to the meeting of June 14, 2001 between representatives of the Division of Anti-Infective Drug Products and GlaxoSmith Kline. In this meeting, we discussed the draft labeling for *Augmentin ES* (amoxicillin/clavulanate potassium) Powder for Oral Suspension. This product is in the final stages of review in the Division. Importantly, the participants in the meeting reached a tentative agreement on revised draft labeling and we submitted the WORD file reflecting this tentative agreement on June 15, 2001. We understand from Dr. Korvick's statements that the draft labeling, as submitted on June 15, will undergo a final review by yourself and Dr. Murphy.

The purpose of this letter is to respond to an additional, important topic raised by the Division's team in the meeting of June 14. The Division advised GSK of concerns regarding the proprietary name, Augmentin ES, for this powder for oral suspension product. Our understanding of FDA's points is as follows:

1. The proprietary name "Augmentin ES" for the oral suspension product (supplying 600mg amoxicillin/5mL of suspension) conflicts with use of the name Augmentin ES 1000mg/62.5mg Tablet proposed by GSK for the new tablet product (as submitted to FDA in NDA 50-785 on December 20, 2000).

2. The ES suffix in Augmentin ES could signify "extra strength" or an alternative meaning (the example of "extended spectrum" was stated). It was not clear to the Division whether there is a precedent with prescription drug products for a standard meaning of the suffix ES.

3. Some members of the Division stated the preference that GSK continue use of the "numbering system" to identify each specific strength of product in the Augmentin product line.

DUPLICATE

We propose to address each of these points in the remainder of this submission.

Point 1: The proprietary name "Augmentin ES" for the oral suspension product (supplying 600mg amoxicillin/5mL of suspension) conflicts with use of the name Augmentin ES 1000mg/62.5mg Tablet proposed by GSK for the new tablet product (as submitted to FDA in NDA 50-785 on December 20, 2000).

We understand this concern and do not want to have a situation where use of the same proprietary name for two distinct dosage forms could lead to confusion or possible medication errors. Therefore, we are hereby withdrawing the proprietary name, Augmentin ES, from NDA 50-785 for the tablet product under ongoing review in your Division; we are also stating our intent to submit a formal amendment to NDA 50-785 in order to withdraw the name Augmentin ES from that NDA and propose a different proprietary name for the tablet product. This decision by GSK is also consistent with the "first-in, first-out" approach that has been applied historically by reviewing Divisions, the Labeling & Nomenclature Committee, and most recently by the Medication Errors group within OPDRA. In view of this decision by GSK, we have removed the potential conflict for Augmentin ES. Therefore, we believe that this specific point should be considered resolved so as to no longer be an obstacle to use of the name "Augmentin ES" for the powder for oral suspension in NDA 50-755.

Point 2: The ES suffix in Augmentin ES could signify "extra strength" or an alternative meaning. It was not clear to the Division whether there is a precedent with prescription drug products for a standard meaning of the suffix ES.

The ES suffix has not been used on many different prescription drug products. However, to our knowledge, the ES suffix has been used for two FDA-approved prescription drug products, one of which has been very extensively prescribed in the United States for several years. For both products, ES means "extra strength" - - the same meaning intended for its use in Augmentin ES. The following paragraphs summarize the information on these precedent products.

Vicodin ES Tablets comprise an extra strength, combination, prescription tablet product containing acetaminophen plus hydrocodone. Each Vicodin ES Tablet contains acetaminophen 750mg plus hydrocodone 7.5mg. (For comparison, a Vicodin Tablet contains acetaminophen 500mg plus hydrocodone 5mg.) Importantly, for this discussion of ES and its meaning as "extra strength", the extensive use of Vicodin products in the United States has facilitated knowledge of the ES suffix as meaning "extra strength". Specifically, bioequivalent generic products for Vicodin and Vicodin ES Tablets were the #1 dispensed drug product in the United States in 2000 with approximately 57,000,000 prescriptions written (*2001 Drug Topics Red Book*, page 160). This very high volume of prescribing ([redacted] more prescriptions than the #1 prescription patent-protected product) for this widely known product, which has been on the US market for over 10 years, has established the ES suffix as extra strength.

Tuss-ES Syrup is the other product that uses the ES suffix. Tuss-ES Syrup comprises an extra strength, combination, prescription product containing chlorpheniramine maleate, hydrocodone, and phenylephrine. Each 5 mL of Tuss-ES Syrup contains chlorpheniramine maleate 2mg, hydrocodone 6mg, and phenylephrine 5mg. (For comparison, each 5 mL of Tuss-HC Syrup contains chlorpheniramine maleate 2mg, hydrocodone 2.5mg, and phenylephrine 5mg.)

We are not aware of any other prescription drug product that uses the ES suffix. Since the ES suffix has only been used to mean "extra strength", and since the extensive prescribing of Vicodin ES has helped to reinforce this meaning of ES for many years in the United States, we believe that the name, Augmentin ES Powder for Oral Suspension, can properly denote the new product providing 600mg amoxicillin/5mL of suspension.

Point 3: Some members of the Division stated the preference that GSK continue use of the "numbering system" to identify each specific strength of product in the Augmentin product line.

We understand the preference by the Division to continue use of the "numbering system" for various Augmentin products. Based on the meeting of June 14, some of us at GSK had the impression that the Division may incorrectly perceive that GSK will use either the proprietary name "Augmentin ES" or a numbering system to identify this new powder for oral suspension. In fact, GSK has proposed draft labels, cartons, and labeling that show that we plan to use **both** the proprietary name (Augmentin ES) and our long-standing numbering system to clearly identify this specific product. In the interest of clarity and a shared understanding, allow us to provide the following summary table to show exactly how the currently approved suspension products and the new product are described in the HOW SUPPLIED section of their respective labeling.

Product	**HOW SUPPLIED** section of labeling
Augmentin® 125 mg/5 mL for Oral Suspension	*"Each 5 mL of reconstituted banana-flavored suspension contains 125 mg amoxicillin and 31.25 mg clavulanic acid as the potassium salt."* 75, 100, and 150 mL bottles
Augmentin® 200 mg/5 mL for Oral Suspension	*"Each 5 mL of reconstituted orange-raspberry-flavored suspension contains 200 mg amoxicillin and 28.5 mg clavulanic acid as the potassium salt."* 50, 75, and 100 mL bottles
Augmentin® 250 mg/5 mL for Oral Suspension	*"Each 5 mL of reconstituted orange-flavored suspension contains 250 mg amoxicillin and 62.5 mg clavulanic acid as the potassium salt."* 75, 100, and 150 mL bottles
Augmentin® 400 mg/5 mL for Oral Suspension	*"Each 5 mL of reconstituted orange-raspberry-flavored suspension contains 400 mg amoxicillin and 57 mg clavulanic acid as the potassium salt."* 50, 75, and 100 mL bottles
Augmentin ES™ 600 mg/5 mL for Oral Suspension	*"Each 5 mL of reconstituted orange-raspberry-flavored suspension contains 600 mg amoxicillin and 42.9 mg clavulanic acid as the potassium salt."* 50, 75, 100, and 150 mL bottles

Consistent with the HOW SUPPLIED section of labeling, the immediate label of each bottle specifies (in very prominent type) the concentration of amoxicillin provided in the reconstituted product (i.e., 125, 200, 250, 400, or 600 mg/5mL).

Therefore, as illustrated above, NDA 50-755 includes labels and labeling showing that we plan to use **both** the proprietary name (Augmentin ES) and our long-standing numbering system to clearly identify the new product. We believe that use of both the numbering system and a suffix are important to provide two ways to readily distinguish this specific product from other Augmentin products. We also believe that the information provided here, summarizing our continued use of the numbering system on labels and in labeling, adequately addresses the Division's concern. Therefore, we request that you consider this point resolved so as to no longer be an obstacle to use of the name "Augmentin ES" for the powder for oral suspension in NDA 50-755.

Additional Comments:
GSK believes that there is practical value to health care professionals, GSK, and FDA from use of a unique proprietary name (Augmentin ES) for the new 600mg/5mL product.

- The unique proprietary name, Augmentin ES, will help to clearly distinguish this product, which has labeling that is different from the labeling of other amoxicillin/clavulanate products. Only Augmentin ES Powder for Oral Suspension has labeling for use at a dose of 90mg/kg/day, based on the amoxicillin component, for certain pediatric patients.
- The unique proprietary name, Augmentin ES, provides a means of assuring that any advertising and promotional labeling on this product is very clearly identified with the 600mg/5mL product, with its unique labeling.

The Augmentin ES proprietary name was first proposed for this 600mg/5mL product in our submission to NDA 50-755, dated October 12, 1998. Since that time, GSK has had discussions in good faith with the Division of Anti-Infective Drug Products, including a teleconference on July 19, 2000 for the specific purpose of reaching closure on the proposed proprietary name (following a consult to DAIDP from the Labeling & Nomenclature Committee). At that time, Dr. Gary Chikami was the Director of DAIDP and he led the Division's efforts in the teleconference with personnel from SmithKline Beecham. Importantly, following a productive discusssion, the sponsor was advised that the Augmentin ES proprietary name was acceptable for this product. This decision is captured in the Division's minutes of the discussion; the paragraph containing the Division's decision is quoted below:

> "**Conclusion:** The Agency decided to accept the name Augmentin ES since there is no safety issue and the Sponsor reported that there are no plans at this time to develop another higher strength product."

In view of this documented acceptance of the Augmentin ES name by the Division, and GSK's efforts (as documented above) to remove any perceived conflict with the name of the tablet product (under NDA 50-785) and address the Division's other concerns, we believe that it is reasonable and appropriate for the Division to proceed to a final action of NDA 50-755, with Augmentin ES as the proprietary name. We will be pleased to discuss this matter further, at the Division's request.

This submission is provided in duplicate to NDA 50-755. A desk copy of this submission has been provided via e-mail to Dr. Susmita Samanta for use by the Division. Please call Dr. Cynthia D'Ambrosio (phone: 215-751-3468) for any matters regarding this application. Thank you.

Sincerely,

David M. Cocchetto, Ph.D.
Vice President
Regulatory Affairs

Cynthia D'Ambrosio, Ph.D.
Director

APPEARS THIS WAY
ON ORIGINAL

GlaxoSmithKline

June 11, 2001

NDA 50-755
Augmentin ES™ (amoxicillin/clavulanate potassium)
Powder for Oral Suspension

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Janice Soreth, M.D.
Acting Director, Division of Anti-Infective Drug Products
Food and Drug Administration
HFD-520
Attention: Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: **Revised Draft Labeling for Discussions on June 13-14, 2001**

Dear Dr. Soreth:

Reference is made to NDA 50-755 for Augmentin ES; this application is under active review in your Division. Please refer to the WORD file of revised draft labeling of May 25, 2001 provided by Dr. Susmita Samatha on behalf of your review team to Dr. Cynthia D'Ambrosio. Please also refer to the teleconference of June 5, 2001 between members of your Division and personnel at GlaxoSmithKline. The primary purpose of this teleconference was for you and your colleagues to share with us the thinking and priorities, from a Divisional perspective, around key aspects of the review team's revised draft labeling of May 25. In the teleconference of June 5, we in GSK accepted the action items of providing to Dr. Brittain any specific items of clarification that would assist us in reproducing FDA's analyses of Study 536 and providing Dr. Samanta with GSK's revised draft labeling for discussion at follow-up times with DAIDP on June 13 (10:00-11:30 a.m.) and June 14 (3:30-5:00 p.m.). Earlier today, Dr. D'Ambrosio sent via e-mail to Dr. Samanta (for Dr. Brittain's attention) a separate list of 6 items for clarification. Today, we are herewith submitting GSK's revised draft labeling for further discussion on June 13 and 14. It is our objective to attain approval for this application as a final action by June 22.

Attachment 1 contains GSK's proposal of revised draft labeling for Augmentin ES. As agreed in the teleconference of June 5, the "base" copy in the WORD file is FDA's draft labeling of May 25, 2001. All changes in text and tables from that base copy are shown using "track changes", and these changes are highlighted by vertical bars in the right-hand margin, as well as underlining of new information. Explanatory notes for the highlighted changes are provided in Attachment 2.

3 page(s) of revised draft labeling has been redacted from this portion of the review.

Closing Remarks

We appreciate your willingness to discuss this proposed draft labeling with us via teleconference on June 13 (10:00-11:30 a.m.), with subsequent discussion in a meeting at Corporate Boulevard on June 14 (3:30-5:00 p.m.). After lengthy and energetic discussions within our company, we do believe that the enclosed draft labeling presents prescribing information that will be the basis for safe, effective, and appropriate use of Augmentin ES. We look forward to our discussions.

This submission is provided in duplicate to the Document Control Room. Desk copies were transmitted via secure electronic mail directly to Dr. Susmita Samanta for use by the review team. Please contact Dr. Cynthia D'Ambrosio (phone: 215-751-3468) for any matters regarding this submission. Thank you.

Sincerely,

David M. Cocchetto, Ph.D.
Vice President
Antiviral/Antibacterial Regulatory Affairs

Cynthia D'Ambrosio, Ph.D.
Associate Director

enclosure (Attachment 1 & Attachment 2)

May 22, 2001

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NDA ORIG AMENDMI

NDA 50-755
Augmentin ES™ (amoxicillin/clavulanate) 14:1 Suspension

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Subject: Revised Draft Package Labeling

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA) for *Augmentin ES™* (amoxicillin/clavulanate potassium) 600 mg/5mL, powder for oral suspension, as amended April 5, 2000 and December 15, 2000. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline.

Reference is also made to correspondence dated July 27, 2000 in which SB submitted container labels for the professional sample product.

At this time, SB is submitting a revised version of the sample carton labeling. The revised label has the words "Orange Raspberry Flavor" printed on the carton. There are no changes to the labeling on the 5mL 1-dose vials that each carton will contain.

If you have any questions or need further information about this submission, please contact me at 215-751-6318 (phone) or 215-751-4926 (fax).

Sincerely,

Deneen Stewart

Deneen Stewart
Senior Regulatory Associate
U.S. Regulatory Affairs

Copies:
Original (1)
NDA archival copy (1)
Desk copy: Dr. Susmita Samanta (Regulatory Project Manager)
Dr. David Katague (Chemistry Reviewer)

April 19, 2001

NDA 50-755
Augmentin ES™ (amoxicillin/clavulanate potassium) 14:1 suspension

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Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Subject: Revised Draft Labeling

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceuticals' (SB's) New Drug Application (NDA) for *Augmentin ES™* (amoxicillin/clavulanate potassium) 600 mg/5 mL, powder for oral suspension, as amended on April 5, 2000 and December 15, 2000. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline.

Reference is also made to correspondence dated February 1, 2001 in which SB provided a summary of the recommendations from the Anti-Infective Drugs Advisory Committee meeting on January 30, 2001, to our revised Draft Labeling submission of March 2, 2001, and to the Division's response to that submission of March 29, 2001.

At this time we are submitting newly revised Draft Labeling for the Division's consideration. The revised Draft Labeling reflects the majority of the recommendations presented in the Division's response to our previous labeling proposal. Once the Division has had an opportunity to review the current submission, we request a teleconference to resolve any remaining issues.

For ease of review and discussion, the revised Draft Labeling is provided in two text formats. Attachment 1 contains the Proposed Labeling text. Attachment 2 contains a comparison of our new Proposed Labeling text to the Division's proposed text of March 29, 2001. Within this document, new text is underlined, and deleted text is noted by strikethrough. A rationale supporting our proposed revisions is provided in Attachment 3. The rationale document also includes several requests for clarification of items in the Division's response of March 29, 2001. The supporting tables, listings and publications

that are cited in the rationale are contained in Attachment 4. This information is provided in duplicate.

As a review aid, this submission also is provided in electronic format. All documents are provided as electronic files in Portable Document Format (PDF). In addition, the new Proposed Labeling text is provided in Microsoft® Word (.doc) format. The review aid has been organized in a folder-based structure in compliance with the January 1999 guidance for providing regulatory submissions in electronic format. A description of the folder contents is provided below.

Description	Folder name	Filename
Attachment 1 Proposed Labeling	N050755\labeling	[redacted]
Attachment 2 Proposed Labeling - compare version	N050755\labeling	[redacted]
Attachment 3 Rationale	N050755\labeling	[redacted]
Attachment 4 Supporting Documents	N050755\labeling\pubs	---

For further information about this submission, or to arrange a teleconference, please contact me at 215-751-3468 (phone) or 215-751-4926 (fax).

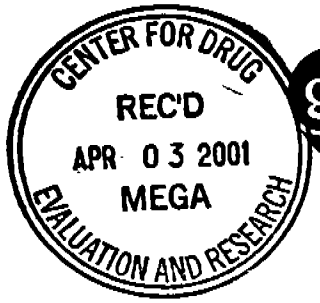
Sincerely,

Cynthia D'Ambrosio

Cynthia D'Ambrosio, Ph.D.
Associate Director
U.S. Regulatory Affairs

Copies:
Original (1)
NDA archival copy (1)
Review aid: Dr. Susmita Samanta, Regulatory Project Manager

ORIG AMENDMENT
BP



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March 30, 2001

NDA 50-755
Augmentin ES™ (amoxicillin/clavulanate potassium) 14:1 suspension

Janice Soreth, M.D. Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Subject: 25000/574 – Final Clinical Pharmacology Report

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA) for *Augmentin ES*™ (amoxicillin/clavulanate potassium) 600mg/5ml, powder for oral suspension, submitted October 31, 1997 and amended on April 5, 2000 and December 15, 2000. SmithKline Beecham is a wholly owned subsidiary of GlaxoSmithKline.

Reference is also made to the Study 574 interim report, "A study to determine the pharmacokinetic profiles of amoxicillin and clavulanate over a 12 hour dosing interval in paediatric patients in the weight range of 5 to 40 kg receiving Augmentin at 45/3.2 mg/kg orally every 12 hours for up to 10 days" [SB Document Number [redacted], submitted December 15, 2000.

Please find enclosed the Study 574 final Report, "A study to determine the pharmacokinetic profiles of amoxicillin and clavulanate over a 12 hour dosing interval in paediatric patients in the weight range of 5 to 40 kg receiving Augmentin at 45/3.2 mg/kg orally every 12 hours for up to 10 days: Final clinical Pharmacology Report" [SB Document Number [redacted]], issued on December 15, 2000.

The final report for Study 574 contains the safety results from the study along with the pharmacokinetic information that was submitted on December 15, 2000.

ORIGINAL

If you have any questions or need further information about this application, please contact me at 215-751-3468.

Sincerely,

Dennis R. Stewart
for

Cynthia D'Ambrosio, Ph.D.
Associate Director
U.S. Regulatory Affairs

Copies:
2 Review copies
1 Archival copies
Desk copy: Dr. Sumita Samanta