CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-747

50-748

CORRESPONDENCE

[illegible] DATE

ORIG AMENDMENT

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
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September 5, 1997

Gary Chikami, 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
3rd Floor, Room N303
Rockville, MD 20857

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-748

ORIGINAL NEW DRUG APPLICATION

Dear Dr. Chikami:

In accordance with Sections 507(e) and 505(b)(1) of the Federal Food Drug and Cosmetic Act, Rhône-Poulenc Rorer Pharmaceuticals Inc. (RPR) is submitting an Original New Drug Application for Synercid® (quinupristin/dalfopristin) I.V. This New Drug Application demonstrates the efficacy and safety of Synercid in the treatment of complicated skin and skin structure infections, [redacted]

Because of the nature of the different indications sought for Synercid, the Division of Anti-infective Drug Products (DAIDP) felt it was administratively advantageous for them to receive two separate applications. Therefore, we are also submitting today, under separate cover, another New Drug Application for Synercid (NDA 50-747). That application demonstrates the efficacy and safety of Synercid in the treatment of infections due to VREF (Vancomycin-resistant *Enterococcus faecium*) including cases associated with concurrent bacteremia and infections caused by *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), in patients failing other therapies including cases associated with concurrent bacteremia.

DAIDP and RPR agreed to the format and content of the attached NDA at a November 6, 1996, pre-NDA meeting (minutes submitted to DAIDP on November 15, 1996).

In accordance with Section 736(a)(1)(B)(i) of the Prescription Drug User Fee Act of 1992, RPR sent a check [redacted] to the Food and Drug Administration, Pittsburgh, Pennsylvania on August 28, 1997. The Food and Drug Administration assigned the application the User Fee Identification Number 3317.

In accordance with Section 306(k)(1) of the Federal Food Drug and Cosmetic Act, we hereby certify that, in connection with this application, RPR did not and will not use in any capacity the services of any person debarred under the Mandatory Debarment provisions [Section 306(a)] or the Permissive Debarment provisions [Section 306(b)] of the Federal Food Drug and Cosmetic Act in connection with this application.

In accordance with 21 CFR §314.50(d)(1)(v), RPR certifies that a field copy of this application meeting the requirements of 21 CFR §314.50(k)(3) is being sent to our home FDA district office in Philadelphia, Pennsylvania.

RPR considers the information in this application confidential and proprietary. We request, therefore, that no portions of this application be disclosed to third parties under FOI or otherwise, without first obtaining RPR's written consent.

If you have any questions please do not hesitate to contact me or Mr. Mark Learn at (610) 454-3053.

Sincerely yours,

John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs

JJS:MDL/mdl

APPEARS THIS WAY
ON ORIGINAL

RHÔNE-POULENC RORER

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March 4, 1998

VIA FACSIMILE

Gary Chikami, M.D., Director
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Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747

Outline for Confirmatory Protocol

Dear Dr. Chikami:

In follow-up of our teleconference on 26 February 1998, attached please find the draft synopsis for the confirmatory clinical study.

Rhône-Poulenc Rorer acknowledges that for approval of Synercid® for the indication of vancomycin-resistant *Enterococcus faecium* (VREF) infection under subpart H, an additional clinical trial is necessary. However, Rhône-Poulenc Rorer reaffirms its position that the existing data from the emergency-use program have established the clinical benefit of Synercid for treatment of VREF infections. In particular, the Sponsor believes that clearance of bacteremia is not a surrogate marker, in that the study methodology required not only clearance of VREF from the blood, but also resolution of accompanying signs and symptoms of infection plus eradication or presumed eradication of VREF from the primary site(s) of infection. Therefore, clearance of bacteremia is not analogous to reduction of viral burden in HIV infection, in which only a laboratory parameter is assessed as the so-called surrogate marker. In addition, the Sponsor notes that Synercid's effect on mortality was demonstrated in the analyses of delay in treatment initiation, as presented to FDA on 12 February 1998 and to the advisory committee itself on 19 February 1998.

In considering the optimal design of the confirmatory clinical trial, the Sponsor considered existing scientific data, continuing medical need, and FDA's comments regarding the possibility of providing Synercid dose-response data. The current proposed protocol design, which was validated by discussions with external Infectious Diseases experts, reflects the hypothesis that combining Synercid with another active antimicrobial agent will produce an

improved overall response in patients with bacteremic VREF infections. This draft protocol will undergo development and modifications as a result of input from experts.

The specific considerations for the study design are as follows:

1. *In vitro*, animal *in vivo*, and human clinical studies data

In vitro data indicate that Synercid alone is bacteriostatic to modestly bactericidal against isolates of VREF. When a cell-wall active antimicrobial, specifically a beta-lactam, is tested *in vitro* in combination with Synercid, enhancement of activity has been demonstrated. Furthermore, an animal model of VSEF infection (erythromycin-resistant strain) indicated that the addition of a cell-wall active agent (amoxicillin) to Synercid resulted in improved outcome and greater bactericidal activity as compared to either Synercid or amoxicillin alone. Finally, data from the logistic regression analyses of clinical data from the emergency-use program indicate that a successful outcome for VREF infection was associated with concomitant administration of vancomycin, a cell wall-active agent. In contrast, separate regression models have indicated that concomitant administration of chloramphenicol (which could be expected to be antagonistic because of its mechanism of action - inhibition of protein synthesis at the bacterial ribosome) was associated with an outcome of failure.

2. Medical Need

For treatment of serious enterococcal infections, clinicians have generally preferred to administer combination therapy, for example, a beta-lactam or vancomycin in combination with an aminoglycoside when the isolate is not resistant to the beta-lactam and does not exhibit high-level resistance to the aminoglycoside. Because of the design of the emergency-use program, combination therapy could not be studied prospectively. However, at this point in the development of Synercid, the Sponsor believes that clinicians and their patients could benefit from an increase in the knowledge about the efficacy and safety of combination therapy for VREF infections.

3. Desirability of providing dose-response data for Synercid

FDA has indicated that a possible component of this confirmatory clinical trial could be an assessment of a dose-response relationship for Synercid. As reflected in the accompanying study design, the Sponsor believes that varying dose frequency may provide useful confirmatory information and also better highlight the efficacy and safety profile of those regimens, specifically augmenting understanding of the benefit/risk relationship.

Finally, the Sponsor considered whether a comparative study could be performed, as for example, testing Synercid versus chloramphenicol alone or in combination with doxycycline. The Sponsor believes that there are substantial scientific and ethical issues with such an approach. A point made unanimously by the four external experts with whom we validated the study design [redacted] was that an acceptable comparator regimen is not at all obvious and that any choice would be viewed very skeptically by institutional review boards, not to mention investigators who would be asked to enroll patients in such a study.

In view of the above considerations, the Sponsor proposes the attached study, specifically designed with the following hypotheses in mind:

1. Synercid® 7.5 mg/kg q8h will produce an overall response rate of approximately 50% in patients with bacteremic VREF infection
2. The addition of a cell-wall active antibiotic, for example, ampicillin, which enhances Synercid's efficacy *in vitro*, will enhance efficacy *in vivo* via a synergistic or additive effect.
3. Synercid® 7.5 mg/kg IV q12h plus a cell-wall active antibiotic will produce efficacy comparable to that seen with Synercid 7.5 mg/kg IV q8h monotherapy, with the tolerability profile of the combination regimen equal to that of Synercid monotherapy and maybe better.
4. Synercid® 7.5 mg/kg IV q8h in combination with a cell-wall active antibiotic will produce efficacy superior to that of either of the above-noted regimens, with a tolerability comparable to that seen with Synercid® 7.5 mg/kg q8h.

The Sponsor has determined that the clinical study should attempt to show statistically significant superiority of the Synercid® 7.5 mg/kg q8h plus cell-wall active antibiotic regimen to each of the other two regimens. The Sponsor has further assumed that an increment in the Overall Response rate of 20 percentage points would represent a clinically meaningful benefit.

Furthermore, the Sponsor believes that benefit can be determined by assessment of Clinical Response, Bacteriological Response and Overall Response, as would be performed in a clinical trial for a traditional indication.

The Sponsor notes that this is a draft protocol synopsis which must be further validated with external experts.

We look forward to a timely discussion with FDA to validate the acceptability of the proposed study. Please do not hesitate to contact me at (610) 454-5471 or Mr Mark Learn at (610) 454-3053.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

GT/mdl

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NEW CORRESP.
N/2

March 11, 1998

Gary Chikami, M.D., Director
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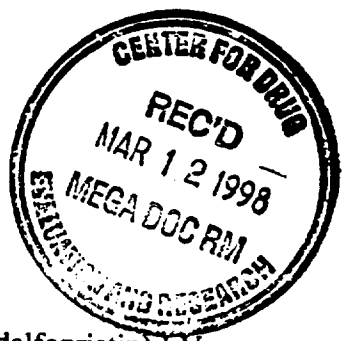

Synercid® (quinupristin/dalfopristin) I.V.

NDA 50-747

Intention to Amend Application

Dear Dr. Chikami:

We acknowledge receipt of your approvable letter dated March 5, 1998, for our new drug application 50-747 for Synercid® (quinupristin/dalfopristin for injection) I.V. submitted under Sections 507(e) and 505(b)(1) of the Federal Food Drug and Cosmetic Act on September 5, 1997. Rhône-Poulenc Rorer plans to amend the application pursuant to 21 CFR 314.110 to provide the information requested in your letter.

We look forward to working with you in the coming weeks to rapidly resolve the outstanding issues regarding this application. If you have any questions about this letter please contact me at (610) 454-5471 or Mr Mark Learn at (610) 454-3053.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MDL/mdl

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April 3, 1998

Gary Chikami, M.D., Director
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Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747
Initial response to March 5, 1998 labeling

Dear Dr. Chikami:

As mentioned during yesterday's teleconference, attached is RPR's initial response to the FDA labeling proposal included with the approvable letter dated March 5, 1998, for our new drug application 50-747 for Synercid® (quinupristin/dalfopristin for injection) I.V. The appended materials include labeling with proposed changes and a two page list of additional comments. The enclosed materials only embody some of RPR's thoughts pertaining to the VREF indication. RPR knows there is missing information in the attached labeling but feel that FDA will benefit from receiving this initial information now. RPR assumes, pursuant to our submission dated March 9 and yesterday's agreement to pursue consensus about the confirmatory trial simultaneously with your endeavors to take an approvable action on the 50-748 application, that we will soon embark on joint labeling discussions of a unified label for all approvable indications.

We look forward to working with you in the coming weeks to rapidly resolve the outstanding issues regarding this application. If you have any questions about this letter please contact me at (610) 454-5471 or Mr Mark Learn at (610) 454-3053.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MDL/mdl

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NC
ORIGINAL

April 14, 1998

Gary Chikami, M.D., Director
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Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747

Outline & Rationale for Confirmatory Protocol

Dear Dr. Chikami:

Pursuant to our teleconference on 2 April 1998, attached please find the draft synopsis and rationale for the confirmatory clinical study. RPR plans to finalize the protocol by the end of May and begin enrollment in December. As shown in the synopsis, enrollment is planned from December 1998 to December 1999. A study report is expected by mid-2000.

We look forward to a timely discussion with FDA to validate the acceptability of the proposed study. Please do not hesitate to contact me at (610) 454-5471 or Mr Mark Learn at (610) 454-3053.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

Attachments

JJS/MDL/mdl

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April 14, 1998

Gary Chikami, M.D., Director
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Synercid® (quinupristin/dalfopristin) I.V.

NDA 50-747

Response to Issues Raised in Approvability Letter

Dear Dr. Chikami:

Below please find RPR's responses to the requests contained in your approvable letter dated March 5, 1998, for our new drug application 50-747 for Synercid® (quinupristin/dalfopristin for injection) I.V.

To help RPR better understand the conclusions reached by FDA with respect to the VREF, [redacted] RPR requests that you provide the criteria for clinical and bacteriologic evaluability and the criteria for treatment outcome (success/failure). Having these criteria will be essential in finalizing the VREF confirmatory trial, and, consequently are requested as soon as possible.

CHEMISTRY

RPR will submit responses to the chemistry issues in the near future.

SUBPART H

. . . the confirmatory protocol must be agreed to with the Agency . . . .

RPR submitted a protocol synopsis for the confirmatory study today under separate cover.

HEPATIC TOXICITY

Prior to approval, a white paper providing a comprehensive assessment of hepatic toxicity should be submitted. This report should address the incidence . . .

The white paper is enclosed as Appendix 1.

The minutes and conclusions of the Synercid Liver Safety Board meetings were submitted April 9, 1998 as part of RPR's response to your March 19 fax.

LABELING

In addition to questions or notations in the draft labeling . . .

RPR submitted an initial response to the FDA labeling proposal on April 3, 1998. In addition to the comments and proposals embodied in that submission, RPR is now proposing the following additional changes to that Synercid labeling submission:

CLINICAL PHARMACOLOGY

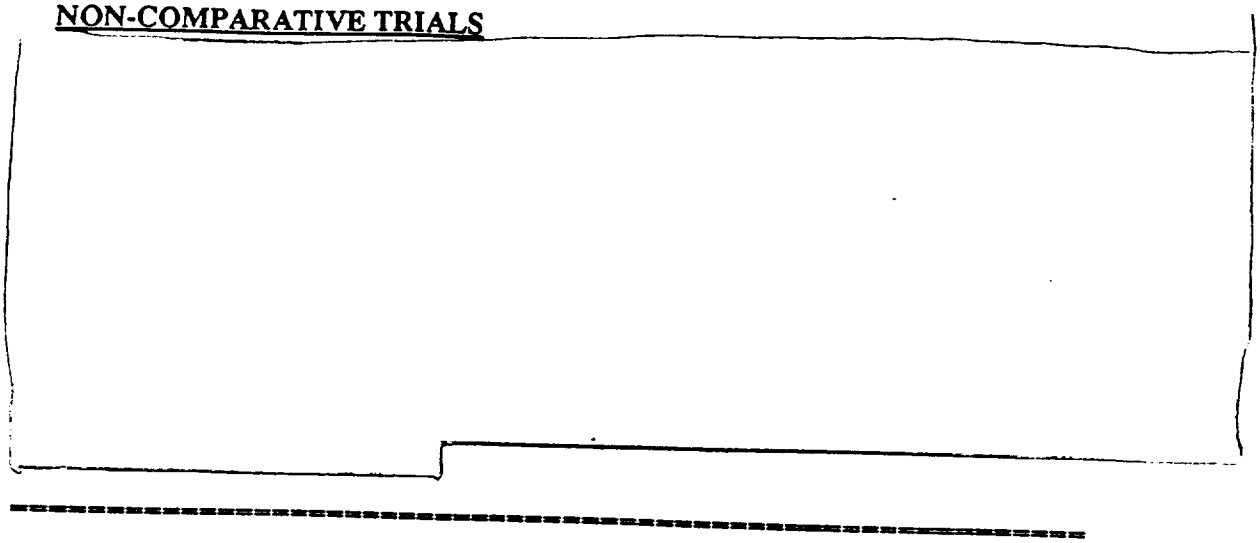
Pharmacokinetics

The protein binding of Synercid is moderate.

ADVERSE REACTIONS

COMPARATIVE TRIALS

NON-COMPARATIVE TRIALS



. . . specific issues which must be addressed include, but are not limited to the following:

1. **The clinical entities of cellulitis, pneumonia, and urinary tract infection are listed as adverse reactions of Synercid administration. Please clarify the classification of these adverse reactions**

   RPR agrees with the FDA that these should not be considered adverse events. Our SOP's and the protocol required that "worsening of (x) condition" be reported as an adverse event thereby including the situation in which (x) was the original infection. Our COSTART coding system did not allow "worsening of" to be captured so the COSTART term became (x)=original infection. In many cases, they were either new infections, recurrence of infections or progression of infections. In some instances, there was clear evidence of superinfection or unrecognized baseline infection. There was also resistance to treatment and prolongation of hospitalization. Our database revealed one serious case of cellulits, and six serious cases of pneumonia. All cases were reported as treatment failure. There were no serious cases of urinary tract infection.

2. **Should the label indicate a maximum absolute dose of Synercid?**

   In the clinical trials, there was no difference in the incidence of non-venous adverse events between obese and non-obese patients. Therefore, a maximum absolute dose of Synercid is not indicated at this time.

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4 The number 30% is not correct. 4.2% of patients had severe related arthralgias and myalgias in the 301 study. (See attached table 12.6.11. appended to this letter as Appendix 2) Sponsor to include the percentage for all the non-comparative studies as this is consistent with the data used for the table of most common events.

5 Integrated Summary of Safety, [Vol. 1.262, p. 432, Table 6.3.6]

6 Integrated Summary of Safety, [Vol. 1.265, p. 48, Table 6.10.5.1]

7 Integrated Summary of Safety, [Vol. 1.266, p. 187, Table 12.2]

3. **Provide the rationale for the WARNING statement "not to be administered as an intravenous bolus."**

RPR has no experience in humans with infusion durations shorter than 30 minutes at 5 mg/kg and 1 hour at the recommended dose of 7.5 mg/kg.

Animal studies revealed that systemic toxicity of a given dose is higher when the dose was administered as a bolus compared to slow infusion. This statement has been added to the label for clarification.

PHASE 4 STUDIES -- CLINICAL

1. **Studies to obtain pharmacokinetic, safety and efficacy data in the pediatric population (0-16 years of age).**

Because of the venous tolerance of RP59500, RPR considers classical phase 1 studies in the pediatric population not to be feasible. RPR will propose a population PK approach to collect PK data in the pediatric patient population during a future trial to evaluate safety and efficacy.

2. **Studies to collect surveillance data on the development of resistance to Synercid (especially among vancomycin-resistant *Enterococcus faecium* strains) and the impact of the resistance on clinical outcomes.**

RPR will collect these data in the proposed confirmatory study. RPR submitted a protocol synopsis and rationale for the confirmatory study today under separate cover. Please see the secondary objectives stated in the protocol synopsis.

PHASE 4 STUDIES -- BIOPHARMACEUTICS

1. **Studies to determine the protein binding *in vivo* and *in vitro*.**

RPR will conduct a further *in vitro* protein binding study in human plasma using a [redacted]

2. **Propose a systematic approach to evaluate important drug-drug interactions.**

Based on *in vitro* studies using human liver microsomes, RP57669/RP54476 (Synercid) has been found to be an inhibitor of the CYP3A4 enzyme. The metabolism rate of the CYP3A4 substrates cyclosporin A, nifedipine, midazolam [redacted] was decreased significantly with respective Ki values which are comparable to the Synercid drug levels achieved following the administration of 7.5 mg/kg. Three *in vivo* drug-drug interaction studies in man with cyclosporin (oral dose), nifedipine (oral dose) and midazolam (iv dose) have been completed. The specific report regarding the interaction study of Synercid with cyclosporine was included in the the NDA filing. The clinical portion of the nifedipine and midazolam interaction studies has been completed, and sample and data analysis are on going.

As soon as these results are available (expected beginning of June), the *in vivo* results (inhibitory potency) will be compared with the *in vitro* findings (Ki) in order to determine if *in vitro* testing can be used to predict the magnitude of the expected *in vivo* drug interaction (at least on a rank order basis). If the results of this correlation are positive (as expected), *in vitro* results will be used to guide the choice of further *in vivo* drug interaction studies. The rationale for the choice of further *in vivo* drug interaction studies with Synercid will be based on the following considerations: narrow therapeutic margin drugs which need to be coadministered with Synercid and are primarily metabolized by the CYP3A4 enzyme. Based on this analysis, the most important drug-drug metabolic interactions will be evaluated *in vivo*.

RPR has also performed an investigation of two other types of drug interaction in order to assess the potency of Synercid to interact with warfarin and digoxin. Regarding warfarin, an *in vitro* protein binding study indicated that Synercid does not modify the human serum protein binding of 2.5 and 5 µg/ml warfarin. Thus, an *in vivo* interaction between Synercid and warfarin due to protein binding interaction is unlikely. Regarding digoxin, an *in vitro* study with Caco-2 cells indicated that Synercid does not have any effect on [3H]digoxin efflux. Thus, Synercid does not significantly inhibit P-glycoprotein efflux of digoxin.

RPR will provide the Agency with the results of ongoing interaction studies and analyses, and provide a list of future proposed *in vivo* drug interaction studies for discussion and agreement.

3. **Studies to evaluate dose adjustments in hepatically impaired patients.**

As discussed at the Advisory Committee meeting, dosage adjustment in special populations is complicated for Synercid due to the number of pharmacologically active components to be considered. RPR previously suggested a dosage reduction from 7.5 mg/kg to 5 mg/kg in hepatically impaired patients if the tolerability of Synercid was not acceptable. This proposed adjustment was based upon the data for dalfopristin-related components. Since dalfoprisitin -related components increased to the smallest degree in hepatically impaired subjects (1.5 fold versus 2.8 fold for quinupristin-related components), the proposed dosage adjustment would lower the exposure to both quinupristin- and dalfopristin-related components in hepatically impaired subjects, but would also maintain dalfopristin-related exposure at comparable levels to that in a typical patient patient administered 7.5 mg/kg. Clearly, this proposal involved extrapolating exposure to a lower dose based upon pharmacokinetic linearity.

RPR would propose to confirm this dosage adjustment in a single dose PK and safety study, at the dose levels of 7.5 and 5 mg/kg, in hepatically impaired subjects with Child Score A and B (8 subjects in each category). An approprite control group will be included. Quinupristin, dalfopristin and their metabolites will be measured in the study.

4. **Submission of the data from your ongoing human pharmacokinetics studies (i.e., lung distribution, renal failure patients, etc.).**

   RPR will provide final reports for the ongoing human pharmacokinetic studies in a timely manner upon sudy completion.

If you have any questions about this letter please contact me at (610) 454-5471 or Mr Mark Learn at (610) 454-3053.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

Attachments

JJS/MDL/mdl

HFD-520 Dillon-Parker

APR 15 1998

NDA 50-747

Rhone Poulenc Rorer Pharmaceuticals
Attention: Mark Learn
Regulatory Affairs
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Mr. Learn:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Synercid® (quinupristin/dalfopristin for injection) I.V.

We also refer to the teleconference between representatives of your firm and FDA on February 26, 1998.

As requested, a copy of our minutes of that teleconference are enclosed.

If you have any questions, please contact Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

RHÔNE-POULENC RORER

BC

ORIG AMENDMENT

ORIGINAL

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May 5, 1998

Gary Chikami, M.D., Director
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Synercid® (quinupristin/dalfopristin) I.V.

NDA 50-747

Response to Issues Raised in Approvability Letter

Dear Dr. Chikami:

Below please find RPR's responses to the CMC requests contained in your approvable letter dated March 5, 1998, for our new drug application 50-747 for Synercid® (quinupristin and dalfopristin for injection) I.V.

1. **Correction of the Current Good Manufacturing Practices (CGMP) deficiencies cited during the Chicago District inspection of the [redacted] facility from November 5 to 24, 1997, must be satisfactorily completed. The CGMP deficiencies noted during the inspection include, but are not limited to, the following:**

   a. [redacted]

   b. [redacted]

   c. **There are no validation data to demonstrate the performance** [redacted]

   RPR Response:

   A meeting was held at the Chicago district office on April 2, 1998. Representatives included Mr. Donald Britt, V.P. Worldwide Quality, RPR, FDA Chicago district, [redacted] and Ms. Lopez, via teleconference from Rockville, CDER Compliance.

   The purpose of the meeting was to discuss the CGMP issues of the approvable letter, i.e. chemistry questions 1 and 2.

a) The [redacted] is currently underway, and will be available for review by the district office on June 1, 1998. The [redacted] are complete and will also be available for review on June 1, 1998. The [redacted] site environmental testing program. A review of the last 12 months data showed no samples out of specification. This will be reviewed by the district office at [redacted] on June 1, 1998. As discussed previously with the district office there were nine user points in the [redacted] which were not routinely monitored. This has now been corrected and all user points are routinely monitored as part of the [redacted] environment monitoring program. This data will also be available for review on June 1, 1998.

b) As previously discussed with the district office, there have been substantial improvements in [redacted] These improvements include:

[redacted]

The data associated with these improvements will be reviewed in detail by the district office on June 1, 1998.

c) As previously committed in the 483 response, [redacted]

2. **In addition to a satisfactory CGMP inspection, requalification (validation) data for** [redacted]

[redacted]

3. **At this time neither the product specification limits nor the retest and expiration dating period has been finalized for the drug substances and drug product,**

respectively. Please submit additional stability data, including statistical analyses on the assay and impurities, on primary stability batches to support the proposed limits and retest/expiration dating period.

Updated stability reports for both drug substances and drug product are included in [redacted] Separate statistical analysis for the drug substances stability data are provided. The statistical analysis for the drug product is included in the stability report.[redacted]

Report Number	Report Title
7696	[redacted]
8068	
7695	
8067	
7693	
7690	

[redacted] For the drug product, the statistical analysis of the data projects a 36 month shelf life, however, RPR requests only a 24 month expiration dating period for the drug product stored at refrigerated conditions (2 - 8°C). Extension of the approved retest/expiration dating period will be based on real time data and will be reported to the Agency in the annual report in accordance with 21 CFR 314.70(d)(5).

4. **Reevaluation of the categorical exclusion of the environmental assessment should be requested if quantities of Synercid are produced beyond that declared [redacted] and for which categorical exclusion was granted.**

RPR confirms that the quantities of Synercid for which the environmental assessment categorical exclusion was granted are correct and the categorical exclusion does not need to be reevaluated. If additional quantities of Synercid are needed beyond that declared, a reevaluation of the categorical exclusion of the environmental assessment will be requested.

In addition, RPR has amended the detailed manufacturing summary for the drug product (NDA section 3.2.3.2) to reflect the process that was validated at [redacted] in March and April, 1998. These improvements to the manufacturing process are designed to minimize the formation of impurities (specifically RP 12536 and RPR 122663), which increase in solution over time[redacted]

[redacted] updated detailed manufacturing summary and further information supporting the modification of the addition of [redacted] slight broadening of the in-process pH control of the compounding solution. The changes to the manufacturing summary are minor in nature and include:

[redacted]

If you have any questions about this letter please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

Attachments

JJS/de

RHÔNE-POULENC RORER

ORIG

ORIGINAL

RHÔNE-POULENC RORER RESEARCH AND DEVELOPMENT
500 ARCOLA ROAD
P O BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

8 June, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)

NDA 50-747

Updated mock carton labeling

Dear Dr. Chikami:

As discussed between Ms. Elicone and Ms. Dillon-Parker, due to the recent changes in the corporate structure of RPR we will implement the use of a new logo which is illustrated on the attached carton label for Synercid for both the 10- and 25- count cartons.

We are providing this artwork to you to ensure that you have the most recent version of our proposed carton label.

If you have any questions about this letter please contact me at (610) 454-5471 or Ms Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
Attachments

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NDA 50-748

JUN 15 1998

Rhone Poulenc Rorer Pharmaceuticals
Attention: Mary Elicone
Regulatory Affairs
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Ms. Elicone:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Synercid® (quinupristin/dalfopristin for injection) I.V.

We also refer to the teleconference between representatives of your firm and FDA on May 19, 1998.

As requested, a copy of our minutes of that teleconference are enclosed.

If you have any questions, please contact Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely yours,

Gary K Chikami

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosed document: 6 pages

Entered to DFS 6/16/98

NDA 50-747

June 3 0 1998

Rhone Poulenc Rorer Pharmaceuticals
Attention: Mark Learn
Regulatory Affairs
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Mr. Learn:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Synercid® (quinupristin/dalfopristin for injection) I.V.

We also refer to the teleconference between representatives of your firm and FDA on April 2, 1998.

As requested, a copy of our minutes of that teleconference are enclosed.

If you have any questions, please contact Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosed document: 5 pages

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

23 July, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747
General Correspondence
Re: Response to 21 July questions

Dear Dr. Chikami,

Following a 21 July telephone conversation with Mr. David Bostwick, please find the following information requested:

1) In RPR's April 14th response to FDA the table on page 2 should be identified as referring to COMPARATIVE studies.

2) The number and percentage of patients with total and conjugated bilirubin 5X ULN in study 398B is 24.9% and 42.0%, respectively.

3) Also in our 14 April, 1998 response to FDA, RPR did not include a table for other significant laboratory values in the ADVERSE REACTIONS non-comparative trials section of the labeling since patients in the non-comparative trials were severely ill and had other underlying disease conditions that contributed to significantly low laboratory values (e.g. 83.8% and 66.7% of patients had significantly low hematocrit and hemoglobin values, respectively*). RPR believes that this would not be useful information for the practitioner.

* Integrated Summary of Safety, [Vol. 1.266, Table 11.15]

If you have any questions regarding this response, please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JS/MEE/mee
k:\anti_inf\ndacorsp\23jul98.doc

RHONE-POULENC RORER

RHÔNE-POULENC RORER RESEARCH AND DEVELOPMENT

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107

MAX W. TALBOTT Ph.D.
VICE PRESIDENT
WORLDWIDE REGULATORY AFFAIRS

TEL. 610-454-5618
FAX: 610-454-2268

July 28, 1998

James M. Timper, Jr.
Chemist
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-520, Room S303
Corporate 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: **NDA 50-747/748, Synercid 500 mg**

Dear Mr. Timper:

Reference is made to the July 27, 1998 telephone conversation between the Agency and Rhône-Poulenc Rorer, to review various issues with Synercid. As we discussed, please find enclosed the following documents:

- Report from Dr. Steven Nail, responding to the FDA's concerns
- Performance Qualifications Summary Report for Synercid

We will be following up with you in a few days to determine if you have any information needs.

In the meantime, if you have any questions concerning this correspondence, please contact me at (610) 454-5618.

Sincerely,

Rhône-Poulenc Rorer

Max W. Talbott, Ph.D.
Vice President
Worldwide Regulatory Affairs

MWT/ae
Enclosures

cc: Dr. Diane Murphy (cover letter only)

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P O BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL 610-454-8000

DESK COPY: M. Dillon-Parker

12 August, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)

NDA 50-747 and NDA 50-748

Response to FDA request: Chemical Compatibility - Final Report

Dear Dr. Chikami:

Pursuant to the NDA submissions for Synercid and the most recent version of the package insert (submitted on 3 April as "Initial response to March 5, 1998 labeling"), attached is the final study report referenced in the footnote of the COMPATIBILITY section of the package insert - page 20.

If you have any questions regarding this submission, please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JS/MEE/mee
attachment

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RHÔNE-POULENC RORER

DESK COPY: ~~Francis Lacame~~

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

26 August 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)

NDA 50-748

Response to FDA comments dated 28 July, 1998 on VREF Confirmatory Protocol (#396)

Dear Dr. Chikami:

In reference to the Division's fax dated 28 July providing FDA's clinical/statistical comments on the revised VREF Confirmatory protocol draft (sent to FDA with 9 June, 1998 correspondence), Attachment A is a summary of RPR's responses to your comments. Attachment B is a copy of the minutes from our first Independent Study Monitoring Board (ISMB) meeting for this protocol. Please note that the statistical responses contained in Attachment B are not the updated version being submitted to FDA in this correspondence. The statistical comments have been updated since the sign-off of the ISMB meeting minutes.

There are several issues (clinical issues #3, #5, #6 and #9 and all statistical issues) for which RPR would like to request further review by FDA. Specifically for the statistical issues, a teleconference with FDA statisticians is requested.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if clarification on this response is needed or for further discussion.

Sincerely yours,

Melicone for JJS

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee

NEW CORRESP

RHÔNE-POULENC RORER

ORIGINAL

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

NC

September 11, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-52
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-748
Intention to Amend Application

Dear Dr. Chikami:

We acknowledge receipt of your approvable letter for Complicated Skin and Skin Structure Infections dated September 4, 1998, for our new drug application 50-748 for Synercid® (quinupristin/dalfopristin for injection) I.V. submitted under Sections 507(e) and 505(b)(1) of the Federal Food Drug and Cosmetic Act on September 5, 1997. Rhône-Poulenc Rorer plans to amend the application pursuant to 21 CFR 314.110 to provide the information requested in your letter. We look forward to working with you to resolve the outstanding issues regarding this indication and further discussion [redacted]

If you have any questions about this letter please contact me at (610) 454-5471 or Ms Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee

RHÔNE-POULENC RORER

DESK COPY TO: Maureen Dillon Parker

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
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TEL. 610-454-8000

16 September 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747

Case Report Form for VREF Confirmatory Protocol (#396)

Dear Dr. Chikami:

Attached is the proposed Case Report Form (CRF) for the VREF Confirmatory Protocol (#396). RPR's response to FDA comments on the revised protocol were sent on 26 August, 1998. We await your final comments in order to proceed with initiation of this protocol.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if clarification on this response is needed or for further discussion.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
Attachment

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RHÔNE-POULENC

DUPLICATE

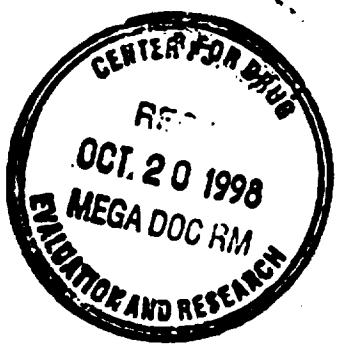
Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

NEW CORRESP

C

19 October, 1998



Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747 and NDA 50-748
Summary of RPR Comments from 01 October teleconference
(RE: NDA 50-748 approvable letter and labeling)

Dear Dr. Chikami:

As agreed during our 01 October teleconference (relative to the approvable letter for NDA 50-748), below are the RPR comments/issues for which further FDA consideration and action are requested:

1) RPR requested that consideration be given to **inclusion of MRSA in the C-SSSI indication**. RPR believes that an adequate number of cases exist in the bacteriologically evaluable population considering the two C-SSSI studies (#304 and #305) and relevant cases in the emergency use program. The table below illustrates RPR's interpretation of the cases:

Study Source	Synercid Outcome (bacterial eradication)	Comparator* Outcome (bacterial eradication)
C-SSSI cases:		
Studies #304 and #305	7/9 (77.8%)	3/6 (50%)
Emergency Use Program 398a and 398b	3/5 (60%)	N/A
Total Skin Cases	**10/14 (71.4%)**	
Bone and Joint Infection Cases:		
Emergency Use Program 398a and 398b	8/10 (80%)	N/A

*Comparators = cefazolin, oxacillin or vancomycin

FDA agreed to re-review the cases and consider this inclusion.

2) RPR requested **specific labeling for Synercid in the clinical studies section:**

"In emergency-use studies, Synercid was used for infections caused by *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains) in patients failing other therapies

3) RPR requests **specific labeling for** *Staphylococcus aureus*) in the *in vitro* or clinical studies section based upon: a) "susceptible" status of all existing strains b) the potential public health concern for this organism; and 3) successful treatment of one case in France (The Lancet, Vol. 351, April 1998). RPR would like to propose the following language:

"Synercid exhibits *in vitro* activity (MICs of 0.25 - 1 µg/ml) *Staphylococcus aureus*) available for examination by the Centers for Disease Control and Prevention. The potential public health impact of such resistance is unknown and the effectiveness of Synercid in treating clinical infections due to has not been established. Other antimicrobial agents have also shown effectiveness *in vitro*."

4) In Hospital-Acquired Pneumonia, RPR understands the current FDA position. However, RPR continues to believe, as did the February 19th Advisory Committee, that for this serious and life-threatening illness, Synercid provides important and meaningful therapeutic benefit to patients with infection caused by *Staphylococcus aureus* for whom no alternative therapy is appropriate. Consequently, RPR requests that FDA The surrogate endpoint is a resolving or stable infiltrate as seen on the chest radiograph. (See data provided in the final study report #306 in NDA 50-748 Volumes 1.244 and 1.245). The confirmatory trial, as required under Subpart H, will resume when the clinical hold is lifted.

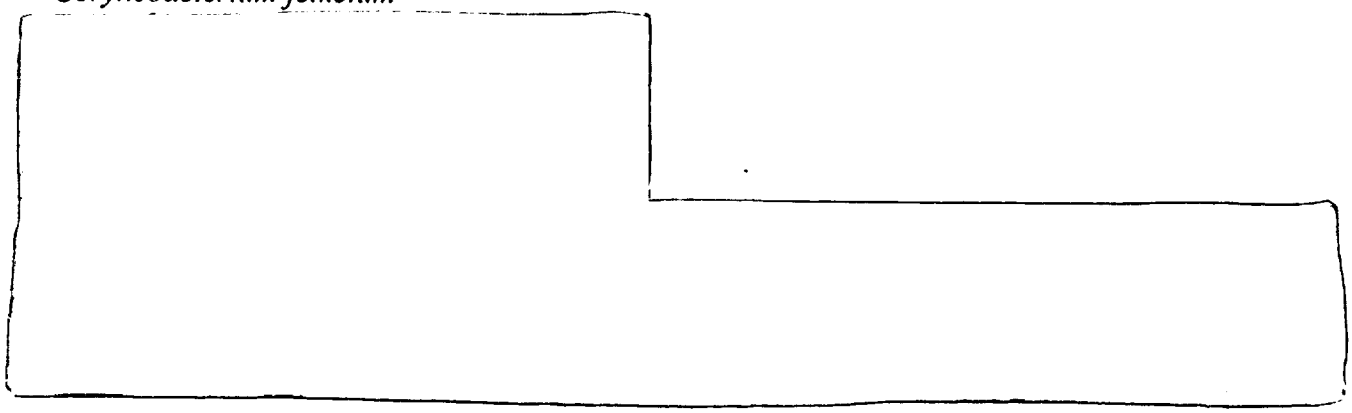
5) RPR has already received confirmation by FDA for the following organisms in the *in vitro*/second list:

Aerobic gram-positive microorganisms
Staphylococcus aureus (including methicillin-resistant strains)
Staphylococcus epidermidis (including methicillin-resistant strains)

Streptococcus agalactiae

RPR requests re-consideration of the following additional microorganisms in the *in vitro*/second list as they are all considered to be relevant pathogens for C-SSSIs:

Aerobic gram-positive microorganisms
Corynebacterium jeikeium



6) RPR believes that there is a **strong medical and public health rationale for the use of Synercid in certain pneumococcal infections and thus proposes the inclusion of *Streptococcus pneumoniae* (including penicillin-resistant and multi-drug resistant strains) in the *in vitro* list** based upon the following: a) available *in vitro* results; b) the role of pneumococcus in the pathogenesis of C-SSSIs (references provided in Attachment A); and c) the necessity to provide practitioners with relevant product information.

Regarding precedent, the meropenem package insert (Attachment B) shows a discrepancy from the stated FDA position that "all pathogens included in the *in vitro* list must be relevant to an approved indication." Meropenem's *in vitro* list includes *Staphylococcus epidermidis* but the product only has clinical indications for intra-abdominal infections and bacterial meningitis.

7) FDA agreed to a re-wording of the C-SSSI indication to remove the reference "limited to" cellulitis and traumatic wound infections. FDA proposed re-wording the indication in C-SSSI to state usage in C-SSSI as "including" cellulitis and traumatic wound infections.

RPR proposes the following wording: "Complicated skin and skin structure infections including cellulitis and traumatic or clean surgical wound infections caused by *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant) or *Streptococcus pyogenes*."

FDA committed to re-evaluate the numbers of cases for "other" infections and schedule a follow-up teleconference with RPR to finalize this issue and the related issue described in #1. RPR also requested that a description of the cases studied be placed in the clinical study section of the labeling under the heading of Complicated Skin and Skin Structure Infections (see table below) for clarity.

"The following table shows the clinical success rate in the clinically evaluable population:

Infection Type	Cured or Improved	
	Synercid (n/N) (%)	Comparator (n/N) (%)
Erysipelas (cellulitis)	78/115 (67.8)	73/108 (67.6)
Traumatic wound infection	58/76 (76.3)	42/61 (68.9)
Clean surgical wound infection	32/52 (61.5)	35/49 (71.4)
Infection complicating peripheral vascular disease	26/45 (57.8)	27/46 (58.7)
Severe carbunculosis	11/12 (91.7)	13/15 (86.7)"

I look forward to receiving your responses on the above. If you have any questions regarding this submission, please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JS/MEE/mee
attachments

Attachment A

References regarding Pneumococcal Skin Infections (* = review articles of particular note):

Hill MD, Karsh J
Invasive soft tissue infections with *Streptococcus pneumoniae* in patients with systemic lupus erythematosus: case report and review of the literature.
Arthritis Rheum 1997 Sep;40(9):1716-9

Le Moal G, et al.
Reduced penicillin-sensitivity pneumococcus arthritis and cellulitis. 2 uncommon sites
Presse Med 1997 Mar 15;26(8):370-1.

Ejlertsen T, et al.
Pneumococcal pyomyositis secondary to pneumonia
Scand J Infect Dis 1997;29(5):520-1

House NS, et al.
Acute onset of bilateral hemorrhagic leg lesions. Pneumococcal cellulitis
Arch Dermatol 1996 Jan;132(1):81-2, 84-5

*Cuenca-Estrella M, Ramos JM, Esteban J, Soriano F
Pneumococcal soft-tissue infections
Clin Infect Dis 1995 Sep;21(3):697-8

Cortes E, Pigrau C, Barbera J, Almirante B
Cellulitis and spondylitis due to *Streptococcus pneumoniae*
Clin Infect Dis 1995 Sept;21(3):696

Kassa A, et al.
Pneumococcal cellulitis
Kinderarztl Prax 1992 Dec;60(9-10):285-7

Molyneux AJ, Judd PA, Jones PH
A fatal case of pneumococcal cellulitis
J Infect 1992 Sep;25(2):238-9

Hammad A, Zittel M, Kalmuk E, Mylotte J
Pneumococcal cellulitis and dysgammaglobulinemia
NY State J Med 1992 Mar;92(3):113-4

Haubrich RH, Keroack MA
Pneumococcal crepitant cellulitis caused by a bronchocutaneous fistula
Chest 1992 Feb;101(2):566-7

*Lawlor MT, Crowe HM, Quintiliani R
Cellulitis due to *Streptococcus pneumoniae*: case report and review
Clin Infect Dis 1992 Jan;14(1):247-50

Peters NS, et al.
Pneumococcal cellulitis: a rare manifestation of pneumococcaemia in adults
J Infect 1989 Jul;19(1):57-9

Verhelst JA, Delvigne C
Pneumococcal osteomyelitis and cellulitis in an adult patient with diabetes mellitus
Diabet Med 1988 May-Jun;5(4):393-5

Young PN, et al.
Cellulitis as a complication of difficult tracheal intubation
Anaesthesia 1987 May;42(5):569

Chartrand SA, et al.
Buccal cellulitis reevaluated
Am J Dis Child 1986 Sep;140(9):891-3

Hinnen RM, Trachtenbarg DE, Miller MA, Coon JJ
Streptococcus pneumoniae cellulitis
IMJ Ill Med J 1986 Aug;170(2):84-6

Dhaene M, et al.
Pneumococcal cellulitis
Am J Emerg Med 1986 May;4(3):225-6

Peyronnet P, et al.
Pneumococcal cellulitis in an immunosuppressed patient
Presse Med 1985 Jun 22;14(25):1386.

Shah B, et al.
Buccal cellulitis
Pediatr Infect Dis 1984 Mar-Apr;3(2):188

Rodloff AC, et al.
Pneumococcal cellulitis
Infection 1983 Nov-Dec;11(6):346

Mujais S, et al.
Pneumococcal cellulitis
Infection 1983 May-Jun;11(3):173-4

Nudelman R, Bral M, Sakhai Y, Wesselius D, Cohen MJ
Violaceous cellulitis
Pediatrics 1982 Jul;70(1):157-8

Shapiro ED et al.
Periorbital cellulitis and paranasal sinusitis: a reappraisal
Pediatr Infect Dis 1982 Mar-Apr;1(2):91-4

Thirumoorthi MC, Asmar BI, Dajani AS
Violaceous discoloration in pneumococcal cellulitis
Pediatrics 1978 Oct;62(4):492-3

Marks JG, et al.
March cellulitis
Mil Med 1978 May;143(5):314-6

Kehne S, et al.
Gingivitis and cellulitis in diffuse pneumococcal infection
South Med J 1978 Apr;71(4):473-4

McGavin CR, et al.
Cellulitis in complicated pneumococcal pneumonia
Br J Dis Chest 1977 Jul;71(3):213-4

Lewis RJ, et al.
Diplococcus pneumoniae. Cellulitis in drug addicts
JAMA 1975 Apr 7;232(1):54-5

Alder R
Letter: Cellulitis: An expected presentation with an unexpected etiology
J Pediatr 1975 Mar;86(3):477-8

Milot J
Orbital cellulitis in children
Union Med Can 1971 Jul;100(7):1351-3.

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
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Tel 610-454-8000

22 October, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747
General Correspondence

Dear Dr. Chikami:

As you know, during the 15-16 October, 1998 Anti-Infective Advisory Committee meetings, various committee members expressed their opinion about the regulatory requirements for approval of anti-infective products for resistant pathogens. Overall, the message from committee members was concordant in that they repeatedly communicated their belief that if the *in vitro* and animal data are consistent, "some" clinical data should be required to gain regulatory approval for products being developed for resistant pathogens.

Considering the opinion of this Advisory Committee and the recommendation of the Advisory Committee on February 19, 1998 that Synercid should be approved for the treatment of VREF infections, RPR requests that FDA reconsider the requirement of another ("confirmatory") VREF trial.

We would greatly appreciate your comments on this issue at our already planned 27 October teleconference (11 AM - 12 Noon) to discuss the confirmatory study.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if clarification on this memo is needed.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mec

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RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
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Tel 610-454-8000

23 November, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747
General Correspondence

Dear Dr. Chikami:

Pursuant to our commitment to comply with the conditions of Accelerated Approval (21 CFR 314 Subpart H) for Synercid NDA 50-747, attached please find the final version of the VREF Confirmatory Study protocol (#396) consistent with CFR 314.510 requirement.

This protocol has been discussed and agreed with the Agency during the last teleconferences on 8 October, 1998 (statistical issues) and 27 October, 1998 (clinical issues).

The study is currently planned to start in March, 1999.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if any further clarification of this memo is needed.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
attachment

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

23 November, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)

General Correspondence

Dear Dr. Chikami:

Pursuant to our commitment to comply with the conditions of Accelerated Approval (21 CFR 314 Subpart H) for Synercid NDA 50-747, attached please find the final version of the VREF Confirmatory Study protocol (#396) consistent with CFR 314.510 requirement.

This protocol has been discussed and agreed with the Agency during the last teleconferences on 8 October, 1998 (statistical issues) and 27 October, 1998 (clinical issues).

The study is currently planned to start in March, 1999.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if any further clarification of this memo is needed.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
attachment

k:\anti_inf\synercid\ndacorsp\cnfprot8.doc

ORIGINAL

N-45S(6C)

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
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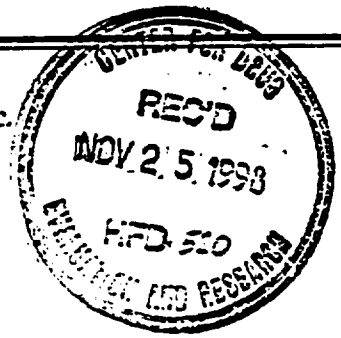
Collegeville, PA 19426-0107
Tel 610-454-8000



23 November, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)

General Correspondence

Dear Dr. Chikami:

Pursuant to our commitment to comply with the conditions of the NDA Approvable Letter dated 4 September, 1998 for Synercid NDA 50-748, please find in Attachment A the final study report of the Population PK Study in Phase III Patients (JRV-135). Submission of this final study report is a **Phase IV commitment** and has also been submitted to NDA 50-748.

Two data diskettes with the study results (as requested by FDA in a fax dated 27 Feb 1996) have been provided in the RPR correspondence to NDA 50-748 dated 23 Nov 1998.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if any further clarification of this memo is needed.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
attachments

RHÔNE-POULENC

Rhône-Poulenc Rorer *Research and Development*

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

11 December, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747
General Correspondence

Dear Dr. Chikami:

Pursuant to NDA 50-747 and our teleconference of 8 December, 1998 to discuss FDA's comments on the final version of the Synercid Confirmatory Protocol (#396) for VREF infections, please find RPR's response to the statistical issues raised.

RPR has incorporated the following FDA statistical comments in the revised protocol:

- Clarifications regarding the interim analyses
- Clarification of stratification analyses
- Additional detailed description of the centralized randomization scheme

RPR believes that a centralized randomization maintaining center level balance is a necessary tool to protect from potential bias. Attachment A is a summary of key arguments for your consideration.

In addition, Attachment B contains the following revised subsections of the study protocol:

- Randomization (section 9.2.2)
- Interim Analyses (section 9.2.4)
- Efficacy Analyses (section 9.3.3)

We would appreciate your written comments or scheduling of a teleconference as soon as possible to allow us to finalize this protocol. We are working to meet the target start date of March, 1999 but will need to have a sign-off in December to achieve that.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if any further clarification of this memo is needed.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
attachments

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

17 December, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747 and NDA 50-748
General Correspondence

Dear Dr. Chikami:

In reference to our correspondence of 16 December, 1998 which contained the revised proposed labeling for Synercid and as previously discussed, RPR would like to request a teleconference in early January to introduce and discuss the major labeling changes/issues (consistent with our 19 October, 1998 correspondence addressing the approvable letter and labeling issues) to facilitate FDA's review of the Synercid package insert.

Attached is the proposed agenda for this meeting. M. Elicone will work with M.Dillon Parker to schedule the meeting.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if any further clarification of this memo is needed.

Sincerely yours,

Mellicone for JJS

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
attachment

Proposed Agenda
Synercid Teleconference
Revised Draft Labeling - Major Changes/Issues

Section of the labeling	Issue
Title Page	Deletion of boxed warning
CLINICAL PHARMACOLOGY-Microbiology	Inclusion of relevant pathogens for Complicated Skin and Skin Structure infections (C-SSSI) in *in vitro* list (*e.g.* [redacted] *Streptococcus pneumoniae*)
INDICATIONS AND USAGE	Wording of VREF indication and C-SSSI
INDICATIONS AND USAGE	Inclusion of MRSA for C-SSSI
ADVERSE REACTIONS-Comparative trials	Removal of: Clinical events-skin and skin structure subsection
ADVERSE REACTIONS-Non-comparative trials	Deletion of listing adverse reactions and laboratory events by individual studies (i.e. 301, 398 and 398B)
CLINICAL STUDIES	Use of RPR's versus FDA's numbers for response rates in VREF, C-SSSI and *Staphylococcus aureus; Staphylococcus aureus* verbiage in this section

[redacted]

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

17 December, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747 and NDA 50-748
General Correspondence

Dear Dr. Chikami:

In reference to our correspondence of 16 December, 1998 which contained the revised proposed labeling for Synercid and as previously discussed, RPR would like to request a teleconference in early January to introduce and discuss the major labeling changes/issues (consistent with our 19 October, 1998 correspondence addressing the approvable letter and labeling issues) to facilitate FDA's review of the Synercid package insert.

Attached is the proposed agenda for this meeting. M Elicone will work with M.Dillon Parker to schedule the meeting.

Please contact me (610-454-5471) or Ms. Mary Elicone (610-454-5859) if any further clarification of this memo is needed.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

JJS/MEE/mee
attachment

Proposed Agenda
Synercid Teleconference
Revised Draft Labeling - Major Changes/Issues

Section of the labeling	Issue
Title Page	Deletion of boxed warning
CLINICAL PHARMACOLOGY-	Inclusion of relevant pathogens for Complicated Microbiology Skin and Skin Structure infections (C-SSSI) in *in vitro* list (*e.g.* GISA, *Streptococcus pneumoniae*)
INDICATIONS AND USAGE	Wording of VREF indication and C-SSSI
INDICATIONS AND USAGE	Inclusion of MRSA for C-SSSI
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CLINICAL STUDIES	Use of RPR's versus FDA's numbers for response rates in VREF, C-SSSI and *Staphylococcus aureus; Staphylococcus aureus* verbiage in this section

16 December, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-748
Response to Issues Raised in Approvable Letter

Dear Dr. Chikami:

Below please find RPR's responses to the requests contained in your approvable letter for Synercid® (quinupristin/dalfopristin for injection) IV dated 4 September, 1998, for our new drug application 50-748.

CHEMISTRY

Satisfactory Establishment Inspection Report

Work is ongoing to address the issues identified during the inspection of the site and to prepare for a reinspection. RPR and [redacted] are in communication with the FDA Compliance Group to keep the FDA apprised of progress on these issues and to agree to the timing for the reinspection of the [redacted] facility. RPR will also submit a briefing package in the very near future to introduce Catalytica Pharmaceuticals Inc., Greenville, NC, as an alternate manufacturing site for Synercid.

DRAFT LABELING

RPR's proposal for the revised labeling is included as **Attachment A. A separate section is included at the end of the proposed labeling for statements originating from new study data which have not been previously submitted. This has been done at the request of FDA in order to allow a first review of the labeling based on already submitted data and then, if timing permits, to allow the review and inclusion of the new information without penalizing the approval timeline.** There are also three supportive documents included as part of the proposed labeling which provide clarification of specific annotations and which are further explained in the table of contents for Attachment A. As

previously requested, RPR would like to schedule a teleconference in early January to introduce and discuss the major labeling changes/issues (consistent with our 19 October, 1998 correspondence addressing the approvable letter and labeling issues) to facilitate FDA's review.

PHASE IV COMMITMENTS

A commitment to conduct a Phase 4 *in vivo* clinical study (ies) to systematically evaluate appropriate drug-drug interactions.

Based on *in vitro* studies using human liver microsomes, RP57669/RP54476 (Synercid) has been found to be an inhibitor of the CYP3A4 enzyme. The metabolism rate of the CYP3A4 substrates cyclosporin A, nifedipine, midazolam [redacted] docetaxel and [redacted] was decreased significantly with Ki values comparable to or lower than Synercid drug levels (Cmax ~ 11 mg/ml) achieved following the 7.5 mg/kg dosage regimen.

Three *in vivo* drug-drug interaction studies in man with cyclosporin (oral dose), nifedipine (oral dose) and midazolam (iv dose) have been completed to date. The rationale for the choice of the drugs co-administered with Synercid was based on the following :
1) drug primarily metabolized by the CYP3A4 enzyme system with a narrow therapeutic margin or with serious side-effects related to overdosage or
2) drug found to be frequently administered in the patients recruited in Synercid phase III trials.

The specific report regarding the interaction study of Synercid with cyclosporine was included in the filing. The two other studies have been completed since the filing, and the reports regarding the interaction studies with nifedipine (JRV 148) and midazolam (JRV 149) are included in this submission (see Attachment C - Revised Draft Label). In summary, the data indicate that co-administration of Synercid resulted in an increase of 25, 18 and 14 % for the Cmax (median values) and an increase of 63, 44 and 38 % for the AUC (median values) of cyclosporine, nifedipine and midazolam respectively.

The applicant believes that Synercid has no effect on the QTc interval, and it was decided for ethical reasons not to perform drug-drug interaction studies with drugs prolonging the QTc interval in man and metabolized by CYP3A4 enzyme, for example : astemizole, [redacted] or cisapride.

The magnitude of the *in vivo* pharmacokinetic interaction of Synercid with drugs mainly metabolized by CYP3A4 enzyme, can now be predicted based on *in vitro* and *in vivo* data available. For high intrinsic clearance drugs, the magnitude will be the highest when the drug is administered orally, and the lowest when the drug is administered intravenously. For low intrinsic clearance drugs, the magnitude of the interaction will be similar for IV and oral routes. This is exemplified when *in vitro* and *in vivo* data obtained with Synercid are compared (see the following table).

SUMMARY OF IN VITRO AND IN VIVO DATA FOR SYNERCID-DRUG INTERACTION

	IN VITRO DATA			IN VIVO DATA			
	Cl int*, µl/min	Synercid Ki, µg/ml	Inhibition type	Route	Increase (%) in AUC	Cmax	Study
Midazolam	[redacted]			IV	42	14	V149
Cyclosporine A				PO	64	25	V138
Nifedipine				PO	44	18	V148
Docetaxel**				IV	NA	NA	-
[redacted]				PO	NA	NA	-
[redacted]				PO	NA	NA	-

*Cl int = Vm/Km (literature data)
** Reports will be available in 1Q99

For cyclosporine and nifedipine, with similar intrinsic clearance values and administered both by the oral route, the *in vivo* interaction was the highest for the drug with the lowest Ki (cyclosporine). Following IV administration of midazolam, a high intrinsic clearance drug, the magnitude of the *in vivo* interaction was comparable to that observed for nifedipine administered orally. This is in agreement with the facts that Synercid exhibits similar *in vitro* inhibitory effects on each drug metabolism rate (similar Kis), and that the drug with a high intrinsic clearance (midazolam) was given intravenously whereas the drug with an intermediate intrinsic clearance (nifedipine) was given by the oral route.

Based on our *in vitro* data for docetaxel [redacted] both drugs for which Synercid Ki values are similar to the Ki for cyclosporin, it can be predicted that the magnitude of the *in vivo* inhibitory effects of Synercid cannot be higher than that observed *in vivo* for cyclosporine administered orally since :
- docetaxel has an intrinsic clearance similar to that of cyclosporine, but is administered by the intravenous route, [redacted] has an intrinsic clearance lower than that of cyclosporine, and is administered orally.

Based on published *in vitro* and *in vivo* data, Synercid is a much weaker inhibitor of CYP 3A4 than ketoconazole and comparable or slightly weaker than itraconazole. Nevertheless, co-administration of Synercid with substrates of CYP 3A4 requires caution and should be accompanied by monitoring of drug levels, when appropriate, for drugs with a narrow therapeutic index and should be avoided for those which can induce QTc prolongation.

One additional drug interaction study is currently planned since a theoretical pharmacokinetic interaction between Synercid and [redacted] can be hypothesized. Firstly, [redacted] is metabolized by CYP 3A4 to the active metabolite [redacted] Thus, co-administration of the two drugs may lead to an

increase in [redacted] levels. Secondly, [redacted] and Synercid are mainly excreted via bile, about two-thirds and three-quarters of the dose, respectively. Cases of hyperbilirubinaemia have been observed following administration of each drug. The precise mechanisms involved in hyperbilirubinaemia are unknown, but competition for biliary excretion at the c-MOAT level with conjugated bilirubin has been hypothesized for both drugs. If Synercid and [redacted] compete for biliary excretion via c-MOAT transporter, then the elimination of [redacted] or/and Synercid may be delayed. To date, there are no *in vitro* or *in vivo* pharmacokinetic data which characterize the mechanisms for a possible interaction between Synercid and [redacted] and assess the magnitude and relevance of an interaction, if any, for patients. RPR's drug interaction study in humans is planned for 1999 to address this issue.

OTHER REQUESTS (NOT REQUIRED FOR APPROVAL)

1. **Commit to conduct:**

   a. **Another protein binding study with modified methodologies.**

   Results of the *in vitro* protein binding study in human plasma [redacted] will be available in 1999. An *in vivo* study will be conducted as part of the **hepatic failure study (#158)** after resolution of the clinical hold. (The #158 **protocol synopsis** is included in **Attachment B**)

   b. A kinetic study to demonstrate the pharmacokinetic relationship between dose and hepatic function. The results of this study may be used as a basis for a dose adjustment recommendation for patients with hepatic impairment.

   As discussed at the Advisory Committee meeting, dosage adjustment in special populations is complicated for Synercid due to the number of pharmacologically active components to be considered. RPR previously suggested a dosage reduction from 7.5 mg/kg to 5 mg/kg in hepatically impaired patients if the tolerability of Synercid was not acceptable. This proposed adjustment was based upon the data for dalfopristin-related components. Since dalfoprisitin-related components increased to the smallest degree in hepatically impaired subjects (1.5 fold versus 2.8 fold for quinupristin-related components), the proposed dosage adjustment would lower the exposure to both quinupristin- and dalfopristin-related components in hepatically impaired subjects, but would also maintain dalfopristin-related exposure at comparable levels to that in a typical patient administered 7.5 mg/kg. Clearly, this proposal involved extrapolating exposure to a lower dose based upon pharmacokinetic linearity.

   RPR will confirm this dosage adjustment in a single-dose PK and safety study (#158), at the dose levels of 7.5 and 5 mg/kg, in hepatically impaired subjects with Child-Pugh Score A and B (6 subjects in each category). An appropriate control group will be included. Quinupristin, dalfopristin and their metabolites will be measured in the study.

   Study #158 is planned to start in 1999 pending resolution of the clinical hold (see **Attachment B for protocol synopsis)**

c. Studies in pediatric patients to obtain information on the appropriate use of Synercid in the pediatric population (e.g. pharmacokinetic, pharmacodynamic, safety data).

Because of the venous tolerance of Synercid, RPR considers classical Phase I studies in the pediatric population not to be feasible. RPR will propose a pediatric development strategy in 1Q99 to collect PK data in a future study/program in order to evaluate safety and efficacy.

2. Submit the population pharmacokinetic study report (results submitted via facsimile on February 10, 1998) for review. Additionally, submit for review the results of the studies regarding lung tissue penetration and the pharmacokinetics of Synercid in patients with renal impairment.

The population pharmacokinetic study report and raw data were submitted to FDA on 23 November, 1998.

Lung tissue penetration data for Synercid are being collected as part of the [redacted] RPR will provide results in a timely manner upon study completion.

The final study report for the pharmacokinetic study in patients with renal impairment (V-143) will be submitted under separate cover, when available, as a Phase IV commitment.

3. Additional analyses of the submitted safety update are necessary. A listing of these requested analyses will be sent under a separate cover.

The **Safety Update** is provided in **Attachment C.**

If you have any questions about this letter please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese, MD, PhD
Director, Regulatory Affairs

Attachments
JJS/MEE/mec

ORIGINAL

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

NEW COMMENT
NC

December 18, 1998

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Room N348
Rockville, MD 20857

RE: Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
Meeting Request

Dear Dr. Chikami:

In NDA 50-747/748 and [redacted] Rhône-Poulenc Rorer (RPR) lists [redacted] as the manufacturing site for Synercid. RPR would like to introduce an alternate manufacturing site (Catalytica Pharmaceuticals Inc., Greenville, NC) for the drug product as soon as possible. In addition, RPR plans to restart the clinical program using the drug product manufactured at Catalytica, after amending the IND with the appropriate CMC documentation to include Catalytica as a manufacturing site.

We respectfully request a meeting with the Agency, to include both the Reviewing Division and the FDA Compliance Division, to discuss our proposed alternate manufacturing site, Catalytica Pharmaceuticals, Inc.. Desk copies of this request are being provided to both Divisions. We would like to have this meeting as soon as possible, preferably the week of January 11, 1999, to discuss the Agency's requirements for the data to be presented in the amendment to NDA 50-747/748 to gain approval for this manufacturing site.

RPR Attendees for this meeting will be:
Bob Barwick, Senior Director, Worldwide Quality Assurance
Ron Dadino, Director, Industrialization US
Donald Esherick, Senior Manager, CMC Liaison, Regulatory Affairs
Greg Sam, Director, Qualification and Validation
Liuda Shtohryn, Senior Director, Worldwide CMC Regulatory Affairs

N50747 Cat

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
Meeting Request
December 18, 1998

A briefing package outlining the drug product manufacture for Synercid at Catalytica is attached. If you have any questions about this meeting request or attached information, please contact me at (610) 454-2636 or Donald Esherick (CMC Liaison) at (610) 454-5757. I will follow up with you before the end of the year to try to schedule this important meeting.

Kind regards,

Rhône-Poulenc Rorer Pharmaceuticals, Inc.

Liuda Shtohryn

Liuda Shtohryn, Pharm.D.
Senior Director
Worldwide CMC Regulatory Affairs

Enclosure

cc: James Timper, Reviewing Chemist
Joseph Famulare, FDA Compliance Division
Mark Lynch, FDA Compliance Division
Michael Verdi, FDA Compliance Division
Debra L. Pagano, Philadelphia District Office
Ballard H. Graham, Atlanta District Office
Raymond Mlecko, Chicago District Office
John J. Savarese, M.D., Ph.D., Senior Director, Regulatory Affairs

ORIGINAL

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

NDA ORIG AMENDMENT
BZ

15 January, 1999

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20857

Synercid® (quinupristin/dalfopristin) I.V.

NDA 50-747

SECOND Response to Issues Raised in Approvability Letter

Dear Dr. Chikami:

Below please find **updated** responses to the requests contained in your approvable letter for Synercid® (quinupristin/dalfopristin for injection) IV dated March 5, 1998, for our new drug application 50-747.

RPR's first response was submitted on 14 April, 1998. New comments for this response are presented in *italics.*

CHEMISTRY

RPR will submit responses to the chemistry issues in the near future.

Responses submitted on 5 May, 1998.

SUBPART H

. . . the confirmatory protocol must be agreed to with the Agency . . . .

RPR submitted a protocol synopsis for the confirmatory study today under separate cover.

Agreement on a final protocol was reached following the joint FDA/RPR teleconference on 21 December, 1998. The final updated protocol is attached.

The final Case Report Form will be submitted in the near future, when available. The target start date for this study is late March/early April, 1999.

Follow-up: During the 8 December, 1998 teleconference, FDA asked whether RPR is aware of any data regarding a potential synergism between cephalosporins and Synercid against VREF (as for MRSA). RPR can now confirm that there are no data describing testing of the combination (cephalosporins and Synercid in VREF) probably due to the expectation that cephalosporins are poorly active versus enterococci.

HEPATIC TOXICITY

Prior to approval, a white paper providing a comprehensive assessment of hepatic toxicity should be submitted. This report should address the incidence . . .

The white paper is enclosed as Appendix 1.

The minutes and conclusions of the Synercid Liver Safety Board meetings were submitted April 9, 1998 as part of RPR's response to your March 19 fax.

No update - response complete

LABELING

In addition to questions or notations in the draft labeling . . .

RPR submitted initial responses to the FDA labeling proposal on April 3, 1998 and April 14, 1998. The final revised labeling is provided in Attachment A of the RPR response to NDA 50-748 approvable letter, dated 16 December, 1998.

. . . specific issues which must be addressed include, but are not limited to the following:

1. **The clinical entities of cellulitis, [redacted] urinary tract infection are listed as adverse reactions of Synercid administration. Please clarify the classification of these adverse reactions**

   RPR agrees with the FDA that these should not be considered adverse events. Our SOPs and the protocol required that "worsening of (x) condition" be reported as an adverse event thereby including the situation in which (x) was the original infection. Our COSTART coding system did not allow "worsening of" to be captured so the COSTART term became (x)=original infection. In many cases, they were either new infections, recurrence of infections or progression of infections. In some instances, there was clear evidence of superinfection or unrecognized baseline infection. There was also resistance to treatment and prolongation of hospitalization. Our database revealed one serious case of cellulitis, [redacted] All cases were reported as treatment failure. There were no serious cases of urinary tract infection.

No update - response complete

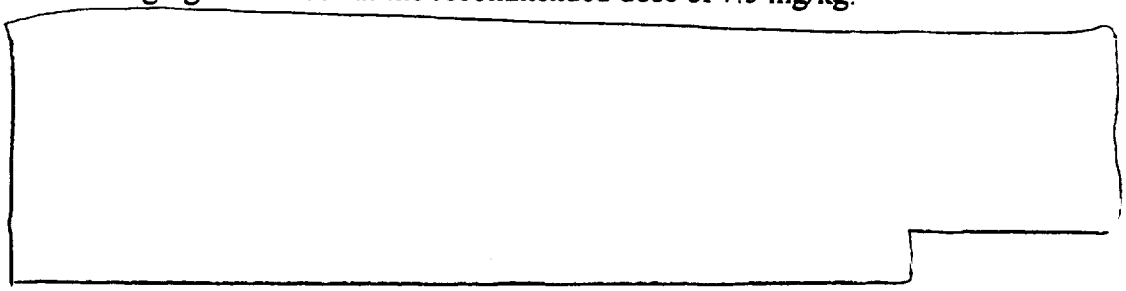
2. **Should the label indicate a maximum absolute dose of Synercid?**

   In the clinical trials, there was no difference in the incidence of non-venous adverse events between obese and non-obese patients. Therefore, a maximum absolute dose of Synercid is not indicated at this time.

   No update - response complete

3. **Provide the rationale for the WARNING statement "not to be administered as an intravenous bolus."**

   RPR has no experience in humans with infusion durations shorter than 30 minutes at 5 mg/kg and 1 hour at the recommended dose of 7.5 mg/kg.



PHASE 4 STUDIES -- CLINICAL

1. **Studies to obtain pharmacokinetic, safety and efficacy data in the pediatric population (0-16 years of age).**

   Because of the venous tolerance of RP59500, RPR considers classical phase 1 studies in the pediatric population not to be feasible. RPR will propose a population PK approach to collect PK data in the pediatric patient population during a future trial to evaluate safety and efficacy.

   RPR proposal to be made in 1Q99

2. **Studies to collect surveillance data on the development of resistance to Synercid (especially among vancomycin-resistant *Enterococcus faecium* strains) and the impact of the resistance on clinical outcomes.**

   RPR will collect these data in the proposed confirmatory study. RPR submitted a protocol synopsis and rationale for the confirmatory study today under separate cover. Please see the secondary objectives stated in the protocol synopsis.

   Some data are already provided in the original dossier. Additional data will be collected in the VREF Confirmatory Study (#396). See attachment.

PHASE 4 STUDIES -- BIOPHARMACEUTICS

1. **Studies to determine the protein binding *in vivo* and *in vitro*.**

   RPR will conduct a further *in vitro* protein binding study in human plasma using a [redacted]

   Results of the in vitro protein binding study in human plasma using a [redacted] will be available in 1999. An in vivo study will be conducted as part of a hepatic failure study (#158) after resolution of the clinical hold.

2. **Propose a systematic approach to evaluate important drug-drug interactions.**

   Based on *in vitro* studies using human liver microsomes, RP57669/RP54476 (Synercid) has been found to be an inhibitor of the CYP3A4 enzyme. The metabolism rate of the CYP3A4 substrates cyclosporin A, nifedipine, midazolam [redacted] was decreased significantly with respective Ki values which are comparable to the Synercid drug levels achieved following the administration of 7.5 mg/kg. Three *in vivo* drug-drug interaction studies in man with cyclosporin (oral dose), nifedipine (oral dose) and midazolam (iv dose) have been completed. The specific report regarding the interaction study of Synercid with cyclosporine was included in the NDA filing. The clinical portion of the nifedipine and midazolam interaction studies has been completed, and sample and data analysis are on going.

   As soon as these results are available (expected beginning of June), the *in vivo* results (inhibitory potency) will be compared with the *in vitro* findings (Ki) in order to determine if *in vitro* testing can be used to predict the magnitude of the expected *in vivo* drug interaction (at least on a rank order basis). If the results of this correlation are positive (as expected), *in vitro* results will be used to guide the choice of further *in vivo* drug interaction studies. The rationale for the choice of further *in vivo* drug interaction studies with Synercid will be based on the following considerations: narrow therapeutic margin drugs which need to be co-administered with Synercid and are primarily metabolized by the CYP3A4 enzyme. Based on this analysis, the most important drug-drug metabolic interactions will be evaluated *in vivo*.

   RPR has also performed an investigation of two other types of drug interaction in order to assess the potency of Synercid to interact with warfarin and digoxin. Regarding warfarin, an *in vitro* protein binding study indicated that Synercid does not modify the human serum protein binding of 2.5 and 5 µg/ml warfarin. Thus, an *in vivo* interaction between Synercid and warfarin due to protein binding interaction is unlikely. Regarding digoxin, an *in vitro* study with Caco-2 cells indicated that Synercid does not have any effect on [3H]digoxin efflux. Thus, Synercid does not significantly inhibit P-glycoprotein efflux of digoxin.

RPR will provide the Agency with the results of ongoing interaction studies and analyses, and provide a list of future proposed *in vivo* drug interaction studies for discussion and agreement.

Based on in vitro studies using human liver microsomes, RP57669/RP54476 (Synercid) has been found to be an inhibitor of the CYP3A4 enzyme. The metabolism rate of the CYP3A4 substrates cyclosporin A, nifedipine, midazolam [redacted] docetaxel and [redacted] was decreased significantly with Ki values comparable to or lower than Synercid drug levels (Cmax ~ 11 mg/ml) achieved following the 7.5 mg/kg dosage regimen.

Three in vivo drug-drug interaction studies in man with cyclosporin (oral dose), nifedipine (oral dose) and midazolam (iv dose) have been completed to date. The rationale for the choice of the drugs co-administered with Synercid was based on the following :
1) drug primarily metabolized by the CYP3A4 enzyme system with a narrow therapeutic margin or with serious side-effects related to overdosage or
2) drug found to be frequently administered in the patients recruited in Synercid phase III trials.

The specific report regarding the interaction study of Synercid with cyclosporine was included in the filing. The two other studies have been completed since the filing, and the reports regarding the interaction studies with nifedipine (JRV 148) and midazolam (JRV 149) were included in the 16 December, 1998 submission (see Attachment C - Revised Draft Label) to NDA 50-748. In summary, the data indicate that co-administration of Synercid resulted in an increase of 25, 18 and 14 % for the Cmax (median values) and an increase of 63, 44 and 38 % for the AUC (median values) of cyclosporine, nifedipine and midazolam respectively.

The applicant believes that Synercid has no effect on the QTc interval, and it was decided for ethical reasons not to perform drug-drug interaction studies with drugs prolonging the QTc interval in man and metabolized by CYP3A4 enzyme, for example : astemizole, [redacted] or cisapride.

The magnitude of the in vivo pharmacokinetic interaction of Synercid with drugs mainly metabolized by CYP3A4 enzyme, can now be predicted based on in vitro and in vivo data available. For high intrinsic clearance drugs, the magnitude will be the highest when the drug is administered orally, and the lowest when the drug is administered intravenously. For low intrinsic clearance drugs, the magnitude of the interaction will be similar for IV and oral routes. This is exemplified when in vitro and in vivo data obtained with Synercid are compared (see the following table).

SUMMARY OF IN VITRO AND IN VIVO DATA FOR SYNERCID-DRUG INTERACTION

	IN VITRO DATA			*IN VIVO DATA*			
	Cl int, µl/min*	*Synercid Ki, µg/ml*	*Inhibition type*	*Route*	*Increase (%) in AUC*	*Cmax*	*Study*
Midazolam				*IV*	*42*	*14*	*V149*
Cyclosporine A				*PO*	*64*	*25*	*V138*
Nifedipine				*PO*	*44*	*18*	*V148*
*Docetaxel***				*IV*	*NA*	*NA*	-
[redacted]				*PO*	*NA*	*NA*	-
[redacted]				*PO*	*NA*	*NA*	-

**Cl int = Vm/Km (literature data)*
*** Reports will be available in 1Q99*

For cyclosporine and nifedipine, with similar intrinsic clearance values and administered both by the oral route, the in vivo interaction was the highest for the drug with the lowest Ki (cyclosporine). Following IV administration of midazolam, a high intrinsic clearance drug, the magnitude of the in vivo interaction was comparable to that observed for nifedipine administered orally. This is in agreement with the facts that Synercid exhibits similar in vitro inhibitory effects on each drug metabolism rate (similar Kis), and that the drug with a high intrinsic clearance (midazolam) was given intravenously whereas the drug with an intermediate intrinsic clearance (nifedipine) was given by the oral route.

Based on our in vitro data for docetaxel [redacted] both drugs for which Synercid Ki values are similar to the Ki for cyclosporin, it can be predicted that the magnitude of the in vivo inhibitory effects of Synercid cannot be higher than that observed in vivo for cyclosporine administered orally since :
- docetaxel has an intrinsic clearance similar to that of cyclosporine, but is administered by the intravenous route,
[redacted]

Based on published in vitro and in vivo data, Synercid is a much weaker inhibitor of CYP 3A4 than ketoconazole and comparable or slightly weaker than itraconazole. Nevertheless, co-administration of Synercid with substrates of CYP 3A4 requires caution and should be accompanied by monitoring of drug levels,

when appropriate, for drugs with a narrow therapeutic index and should be avoided for those which can induce QTc prolongation.

- *One additional drug interaction study is currently planned since a theoretical pharmacokinetic interaction between Synercid and [redacted] can be hypothesized. Firstly, [redacted] is metabolized by CYP 3A4 to the active metabolite [redacted] Thus, co-administration of the two drugs may lead to an increase in [redacted] levels. Secondly, [redacted] Synercid are mainly excreted via bile, about two-thirds and three-quarters of the dose, respectively. Cases of hyperbilirubinaemia have been observed following administration of each drug. The precise mechanisms involved in hyperbilirubinaemia are unknown, but competition for biliary excretion at the c-MOAT level with conjugated bilirubin has been hypothesized for both drugs. If Synercid [redacted] compete for biliary excretion via c-MOAT transporter, then the elimination of [redacted] or/and Synercid may be delayed. To date, there are no in vitro or in vivo pharmacokinetic data which characterize the mechanisms for a possible interaction between Synercid [redacted] and assess the magnitude and relevance of an interaction, if any, for patients. RPR's drug interaction study in humans is planned for 1999 to address this issue.*

3. ***Studies to evaluate dose adjustments in hepatically impaired patients.***

As discussed at the Advisory Committee meeting, dosage adjustment in special populations is complicated for Synercid due to the number of pharmacologically active components to be considered. RPR previously suggested a dosage reduction from 7.5 mg/kg to 5 mg/kg in hepatically impaired patients if the tolerability of Synercid was not acceptable. This proposed adjustment was based upon the data for dalfopristin-related components. Since dalfoprisitin-related components increased to the smallest degree in hepatically impaired subjects (1.5 fold versus 2.8 fold for quinupristin-related components), the proposed dosage adjustment would lower the exposure to both quinupristin- and dalfopristin-related components in hepatically impaired subjects, but would also maintain dalfopristin-related exposure at comparable levels to that in a typical patient administered 7.5 mg/kg. Clearly, this proposal involved extrapolating exposure to a lower dose based upon pharmacokinetic linearity.

RPR would propose to confirm this dosage adjustment in a single dose PK and safety study, at the dose levels of 7.5 and 5 mg/kg, in hepatically impaired subjects with Child-Pugh Score A and B (8 subjects in each category). An appropriate control group will be included. Quinupristin, dalfopristin and their metabolites will be measured in the study.

Study #158 is planned to start in 1999 pending resolution of the clinical hold.