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 study completion.

   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] under clinical hold. RPR will provide results in a timely manner upon study [redacted] 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.

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,

Meelicone for JJS

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

JJS/MEE/mee

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

25 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® I.V. (quinupristin and dalfopristin for injection)
NDA 50-747
Outsourcing of the Emergency Use Program

Dear Dr. Chikami:

This is to inform you that RPR is in the process of transferring certain responsibilities for the conduct of the Synercid Emergency Use program [redacted] The transfer will be effective beginning February 16, 1999. Notification of this change will be sent to all Principal Investigators and Pharmacy Departments during the week of 1 February, 1999.

[redacted] will move into a new facility as of 1 March, 1999. The new address and phone number [redacted]

[redacted] is a fully accredited CRO. [redacted] will dedicate six full-time people plus Quality Assurance and Medical (MD) support, as necessary, to the Synercid Emergency Use program.

The only change that FDA will experience with the [redacted] transfer will be that [redacted] will have responsibility for enrollment of pediatric patients. As such, [redacted] will phone FDA to procure approval for enrollment. RPR will maintain responsibility for enrollment of patients needing intrathecal or intraperitoneal administration of Synercid and will continue to contact FDA to procure approval for these patients.

For your information, the following table summarizes the major changes in responsibility which will occur internally:

SUMMARY OF MAJOR RESPONSIBILITIES FOR SYNERCID EMERGENCY USE PROGRAM

Activity	RPR	[redacted]
Primary phone contact for investigative sites		x
Administrative responsibility for processing and maintenance of study documents		x
Recipient of SAE reporting from investigative sites; reporting responsibility to RPR		x
Sponsor documentation of SAE report and reporting responsibility to FDA	x	
Shipment authorization		x
Packaging/labeling/shipment responsibility	x	

[redacted] personnel are currently completing a one month training program at RPR regarding study responsibilities. RPR will monitor the CRO's performance intermittently and will still maintain pager responsibilities as a back-up to the investigative sites and [redacted] as well.

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/mcc

k:anti_inf\synercid\ndacorsp\eusecro.doc

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

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

Dear Dr. Chikami:

As requested by M.D. Parker, below is a description of RPR's current plans and estimated timelines as regards the Synercid program and related US submissions. We greatly appreciate your willingness to discuss these priorities with RPR.

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

cc: L. Shtohryn - RPR Senior Director Worldwide CMC Regulatory Affairs

SYNERCID PROGRAM - Order of Events for FDA Planning

Issue	Submission (description and target date)	Target date for Resolution with FDA	Comments
Issues for Catalytica Alternate Manufacturing Site Submission	Briefing package submitted on 12/18/98	ASAP January 1999	
Labeling Finalization	Revised PI submitted on 12/16/98	March 1999	
RPR resumes Clinical Trials using Supplies Manufactured at Catalytica	IND amendment for Catalytica to be submitted in March, 1999	March/April 1999	Need to confirm that clinical trials may resume at same time as IND amendment (versus imposition of a 30 day review by FDA)
Catheter Related Bacteremia	Amendment and revised protocol (#309) to be submitted in early February in order to fully discuss possibility of a single study and other protocol particulars	March, 1999	PRIORITY to Restart study/ (ies) in April 1999
Resolution of Manufacturing Issues Related to [redacted] leading to approval of NDAs	[redacted] scheduled for April, 1999. RPR anticipates that [redacted]	May 1999 approval of NDAs	
NDA amendment for alternate manufacturing site (Catalytica)	Amendment to be submitted based on agreement with FDA regarding filing requirements	2Q or 3Q 1999 (requesting expedited review)	

COMMITTEE ON SAFETY OF MEDICINES

The Company Secretary
c/o Ms Averil Lauckner
Head of Regulatory Affairs
Rhone-Poulenc Rorer
RPR House
50 Kings Hill Avenue
Kings Hill
West Malling
Kent ME19 4AH

MARKET TOWERS
1 NINE ELMS LANE
LONDON SW8 5NQ
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Leslie.Whitbread@mca.gov.uk

LW/PMC

1 February 1999

Dear Madam

PRODUCT: SYNERCID **M.A. 00012/0328**

As you know, a pre-hearing was held before the Committee on Safety of Medicines on the above product on 28 January 1999. The Committee have asked me to inform you that they would be willing to advise the Licensing Authority that a Marketing Authorisation should be granted but only if you are willing to agree to the following:

1 The Summary of Product Characteristics (SPC) should more accurately reflect the clinical data. In particular,

1.1 In Section 2
The term "*as the mesilate salts*" should be added.

1.2 In Section 4.1
This should be wholly substituted by the following text:

Synercid is indicated for the treatment of the following infections when known or suspected to be caused by susceptible gram-positive organisms, when intravenous therapy is appropriate, and when there are no other antibacterial agents active against the organisms which are suitable for treatment of the infection in the individual patient:

- *skin and soft tissue infections*
- *clinically significant infections due to E. faecium*

(see Sections 4.4 Special Warnings and Special Precautions for Use and 5.1 Pharmacodynamics)

COMMITTEE ON SAFETY OF MEDICINES

- *Synercid should be used in combination with an agent(s) active against Gram-negative organisms if a mixed infection is documented or suspected.*
- *Consideration should be given to official guidance on the appropriate use of antibacterial agents.*

1 3 In Section 4.2

The information related to administration now situated in 4.4 of the revised SPC should be moved to 4.2 so that the entire text before the dosing table reads as follows

- *Synercid should be administered through a central venous catheter in 5% glucose solution over a 60-minute period. The safety and efficacy of an intravenous infusion duration of less than 60 minutes has not been evaluated in clinical trials; shorter administration periods must not be used.*
- *Following completion of the infusion, the vein should be flushed with 5% glucose solution to minimise venous irritation. Flushing with saline or heparin immediately after Synercid administration is not recommended.*
- *Synercid is incompatible with saline solutions.*
- *If necessary in an emergency, treatment may be initiated by peripheral intravenous infusion."*

The dosing table should be modified as follows:

a) The separate reference to *S. aureus* infections should be removed
b) SSTI dosing should be footnoted "*Except when due to macrolide-resistant S. aureus when 8 hourly dosing is recommended*"
c) The footnote "*including cases of bacteraemia*" should be removed

The statement regarding renal insufficiency should be replaced by:
Currently, there are insufficient data to determine whether dose reduction is required in the presence of renal impairment and it is recommended that Synercid be used with caution in these patients (see Sections 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetics).

- This sentence should be repeated in section 4.4 of the SPC

1.4 In Section 4.3

The sentences which were proposed by the applicant for section 4 4 regarding agents which are metabolised by CYP3A4 and which prolong the QTc interval should be moved to 4.3 with modification of the second sentence, relating to agents with a narrow therapeutic window, as follows:
Coadministration of Synercid with any drug(s) metabolised by CYP3A4 for which the therapeutic window is narrow should be avoided unless assays of drug levels and close clinical monitoring are possible.

1.5 In Section 4.4

- The first and second paragraphs proposed should be moved to section 4.2 (see above).

COMMITTEE ON SAFETY OF MEDICINES

- This section should now commence with the following text:
  Some in-vitro studies indicated that the activity of Synercid against S. aureus which are constitutively resistant to macrolides, lincosamides and type B streptogramins (MLS_B-C resistance) is reduced compared with that against isolates which do not possess this mechanism of resistance. In general, the majority of methicillin-resistant S. aureus possess MLS_B-C.

  For skin and soft tissue infections, response rates for infections due to S. aureus with MLS_B-C were better when 8 hourly rather than 12 hourly dosing was employed.

  Therefore, it is recommended that Synercid be administered three times daily whenever a macrolide-resistant S. aureus is to be treated. Pending susceptibility test results, any MRSA should be treated with 8 hourly dosing because of the high likelihood of the presence of macrolide resistance (see Sections 4.2 Posology and Method of Administration and 5.1 Pharmacodynamics).

- The third and fourth paragraphs now proposed should be replaced by.
  Synercid is an inhibitor of CYP3A4. Caution is recommended whenever Synercid is to be coadministered with any drug which is metabolised by this route. The addition of any other drugs which inhibit CYP3A4 should be avoided in these circumstances (see Sections 4.3 Contraindications, 4.5 Interactions with Other Medicaments and Other Forms of Interaction and 5.2 Pharmacokinetics).

- The paragraph regarding conjugated hyperbilirubinaemia should be expanded as proposed for the reference to this phenomenon in section 4.5 (see below)

- The specific risks of superinfection with gram-negative pathogens must be mentioned here.

1.6 <u>In Section 4.5</u>

- A sentence should be added to the second paragraphs proposed by the applicant on the matter of CYP3A4 interactions the effect that
  Coadministration of Synercid with FK-506 (Tacrolimus) resulted in increases in trough levels of this agent by about 15%. In the absence of any other data, it is recommended that assays for FK-506 are performed whenever Synercid is given with this agent.

- The third paragraph proposed is a negative statement and should be removed. such information may be covered in section 5.2 *Pharmacokinetics*

- The fourth (last) paragraph should also state:
  In addition, plasma concentrations of quinupristin metabolites are increased by more than five-fold when total bilirubin exceeds three time the upper limit

COMMITTEE ON SAFETY OF MEDICINES

of normal. It is not known what effect, if any, these increases in exposure to metabolites has on the safety and efficacy of Synercid.

1.7 In Section 5.1

- Paragraphs 1 and 2 should be simplified to.
  The streptogramin A (dalfopristin) and B (quinupristin) components of Synercid are presented for medicinal use in a 7:3 ratio. Quinupristin and dalfopristin each possess in-vitro bacteriostatic activity against many Gram-positive bacterial species and act synergistically to provide bactericidal activity. In addition, the major metabolites of both quinupristin and dalfopristin display synergy with the complementary parent compound in vitro.
  The ways in which the macrolide-lincosamide-streptogramin (MLS) antibacterials, and particularly the A and B streptogramin components, interact at the bacterial ribosome to achieve inhibition of bacterial protein synthesis is complex. Binding of A components to the ribosome is followed by separate binding of B molecules. A stable conformational change in the ribosome occurs and protein synthesis is switched off.

- Paragraphs 3, 4 and 5 should be replaced by.
  There is no cross resistance between Synercid and β-lactams, aminoglycosides, glycopeptides, quinolones, or tetracyclines as measured by MIC.

  Some in-vitro studies have indicated that the activity of Synercid against S. aureus which are constitutively resistant to macrolides, lincosamides and type B streptogramins (MLS_B-C resistance) is reduced compared with that against isolates which do not possess this mechanism of resistance. In general, the majority of methicillin-resistant S. aureus possess MLS_B-C.

  In-vitro combination testing of Synercid with aztreonam, cefotaxime, ciprofloxacin and gentamicin against Enterobacteriaceae and Pseudomonas aeruginosa did not show antagonism. Also, in-vitro combination testing of Synercid with aminoglycosides, β-lactams, glycopeptides, quinolones, tetracyclines and chloramphenicol against enterococci and staphylococci did not show antagonism. However, Synercid antagonised the killing effect of oxacillin and vancomycin against staphylococci and of ampicillin against enterococci.

- The statement re breakpoints should be simplified to:
  The following MIC breakpoints separating susceptible from resistant organisms have been recommended by NCCLS for testing rapidly growing aerobic micro-organisms, including Streptococcus pneumoniae
  Susceptible ≤ 1 μg/mL; Resistant ≥ 4 μg/mL

COMMITTEE ON SAFETY OF MEDICINES

- The table is not acceptable and should be modified as follows:

In vitro antibacterial spectrum	Category with European range of resistance where this is known to vary
Susceptible	
Aerobic Gram-positive micro-organisms:	
*Enterococcus faecium**	
Streptococcus agalactiae	
Streptococcus pneumoniae	
*Streptococcus pyogenes**	
Staphylococcus aureus macrolide-susceptible*	
Staphylococcus aureus macrolide-resistant**	
Intermediately susceptible	
Aerobic Gram-positive micro-organisms:	
Group C streptococci	
Group G streptococci	
Anaerobic micro-organisms:	
Clostridium perfringens	
Peptostreptococcus spp	
Insusceptible (Resistant)	
Aerobic Gram-positive micro-organisms:	
Enterococcus avium	
Enterococcus casseliflavus	
Enterococcus faecalis	
Enterococcus durans	
Enterococcus gallinarum	
Pediococcus spp	
Streptococcus bovis	
Aerobic Gram-negative micro-organisms:	
Enterobacteriaceae	
Gram-negative non-fermenters, incl. Pseudomonas spp.	
Haemophilus influenzae	
Anaerobic micro-organisms:	
Bacteroides spp	
Other *Clostridium* spp	
Fusobacterium spp.	
Prevotella spp.	
Veillonella spp	

* *Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications*

** *Clinical efficacy has been demonstrated in Skin and Soft Tissue Infections*

- The applicant should provide the source data for the % inserted.

COMMITTEE ON SAFETY OF MEDICINES

1.8 In Section 5.2

- The section is long and it would be helpful to insert subheadings
- The data on FK-506 should be added to the section re clinical drug interaction studies.
- The information on quinupristin metabolites should be added to the section on hepatic failure as proposed for other sections of the SPC

1.9 In section 6.6

A warning on the possibility of precipitation in the premix before further dilution should be added and a caution added that if precipitation occurs the product should be discarded

A statement that dissolution of the drug product may take at least two minutes should be added

1.10 In Section 6.4

The statement on the chemical and physical stability of the reconstituted and diluted infusion should appear at the end of section 6.4

1.11 In section 2

The term "*as the mesilate salts*" should be added to Part 2 of the SPC

1.12 In section 7

[redacted] is not a registered trading style in the UK and thus should be deleted.

2. The reconstitution leaflet should be amended in line with the SPC.

3. The patient information leaflet should be amended in line with Directive 92/27 and the approved SPC

4 Product labelling:

A distinct warning should be placed on the product labelling that the reconstituted product should not be administered without prior dilution and a warning should also be given on the route of administration in line with the SPC.

COMMITTEE ON SAFETY OF MEDICINES

M A. 00012/0328

Part II

5 The point regarding room temperature definition and storage condition after reconstitution is considered to be resolved providing room temperature is defined and the storage condition after reconstitution is given in the SPC.

6 The point regarding use of recovered solvents in the drug substance manufacturing process is considered to be cleared if reassurance is given the recovered solvents from other processes are not used in the manufacture of dalfopristin or quinupristin

7 The point regarding control of mycotoxins during the fermentation process has been considered but not adequately addressed. Evidence should be provided that the there is no contamination of mycotoxins at each stage of the fermentation

8 The proposed limit for the residual solvent DCM in dalfoprisin drug substance is not acceptable.

If you wish to discuss the above conditions, please contact the Medical Assessor, Dr M Powell on ext 0486, the Pre-Clinical Assessor, Mr T Berridge on ext. 0391 or the Pharmaceutical Assessor, Mr H Delargy on ext. 0466.

If you are willing to accept the above conditions, please let me know as soon as possible.

Please note that the assessment report is being sent to you in the strictest confidence solely to afford you an opportunity to respond as fully as possible to the points the Committee has raised. You should also be aware that there is a statutory provision on the disclosure of information obtained or furnished pursuant to the Medicines Act.

Please acknowledge receipt of the letter and assessment report.

Yours faithfully

L. Whitbread

L R WHITBREAD
Secretary to the Committee

RHÔNE-POULENC N(469)1m

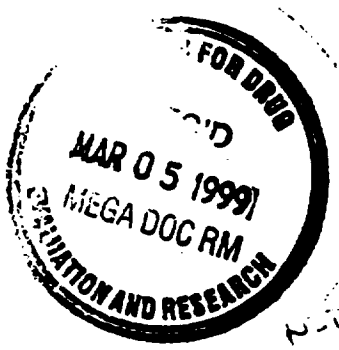
Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

4 March, 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

ORIGINAL



N-750 ATL 1-11-99

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

[redacted]

Final Study Report - Study #132

Dear Dr. Chikami:

Attached is the final study report for Synercid Study #132 ("*A Phase I Open -Label Study of the Plasma and WBC Pharmacokinetics of Multiple Dose Invtravenous RP 59500 in Healthy Male Volunteers*").

A copy of this report is also being submitted to NDA 50-748.

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

cc (memo only [redacted]

Sincerely yours,

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

JJS/MEE/mee
Attachment

N(471)RD GC

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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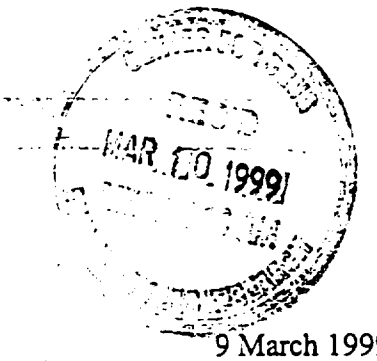
Tel 610-454-8000



9 March 1999

DUPLICATE

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
3rd Floor, Room N303
Rockville, MD 20850

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

General Correspondence -
Response to Queries from FDA Presented During 25 February, 1999 Teleconference

Dear Dr. Soreth:

Attached are responses to FDA queries posed during a joint teleconference on 25 February, 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, M.D., Ph.D.
Senior Director, Regulatory Affairs

JJS/MEE/nrf
Attachment

RESPONSE TO QUERIES FROM FDA PRESENTED DURING 25 FEBRUARY, 1999 TELECONFERENCE

FDA Query #1

Section 6.6 (Prior and Concomitant Medications) of RPR Protocol #396 (VREF Confirmatory Protocol) includes a listing of medications for which Synercid is predicted to cause an increase in plasma concentrations. A. Rakowsky remarked that digoxin and warfarin had been part of that listing in previous protocols and have now been removed. He recalled a submission which had been provided to FDA regarding this issue, but could not detail it specifically.

RPR Response:

RPR provided an explanation of this issue on 14 April, 1998 (Response to NDA 50-747 Approvable Letter). Extracts from that submission, plus additional information is provided below.

Warfarin

An *in vitro* protein binding study indicated that Synercid does not modify the human serum protein binding of 2.5 and 5.0 mcg/ml warfarin. Thus an *in vivo* interaction between Synercid and warfarin due to a protein binding interaction is unlikely.

An *in vivo* interaction based on CYP3A4 inhibition cannot be excluded. This should affect the inactive (or much less active) R-enantiomer of warfarin which is mainly metabolized by CYP3A4 whereas the active S-one is mainly metabolized by CYP2C9. *In vivo* studies published for other drugs show that inhibitory metabolism effects on the R-enantiomers without effects on the S-one do not result in an effect on INR.

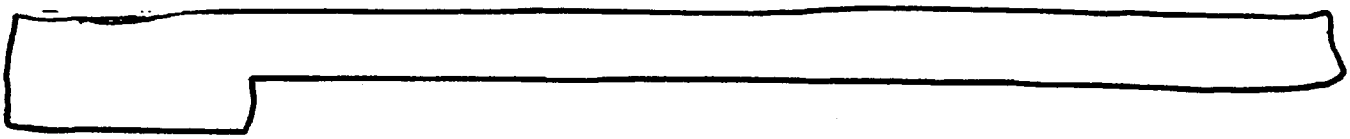
Results of an *in vitro* metabolism interaction study (using human liver microsomes) for Synercid-warfarin enantiomers should be available by the end of March/beginning of April and can be provided to FDA upon request.

Digoxin:

The mechanisms of relevant *in vivo* interactions are based through the effects on P-glycoprotein. 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. In addition, *Eubacterium lentum* present in fecal flora has been shown to be responsible for digoxin metabolism in the gut. Effects of some antibacterial drugs (azithromycin) on digoxin result in digoxin exposure increases in patients. Synercid has low activity on this strain.

In conclusion, the Sponsor does not expect an interaction through either mechanism.

FDA Query #2



RPR Response:

The MITT population:

- will be based on characteristics present at baseline
- major characteristic will be whether presence of disease state is established
- requirement is that the patient received at least one dose of study drug

RHÔNE-POULENC

Rhône-Poulenc Rorer — Research and Development

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

Tel 610-454-5618
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March 26, 1999

Janice Soreth, M.D., Acting Director
Division of Anti-Infective Drug Products (HFD-520)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Room N348
Rockville, MD 20850

RE: Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
Petition for Use of Batches Manufactured

Dear Dr. Soreth:

Reference is made to the letter of August 13, 1998 from Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, specifically items 14-17 on pages 4-5, with respect to Synercid (the letter is provided in the attachment).

The Agency is aware that has worked diligently to complete these items. The information summarizing the review and the recommendation to release the following lots (on an emergency use basis under protocols JRV397 and 398) and were sent to the FDA on the following dates:

Synercid Lot D378061 (CB06489) on March 11, 1999
Synercid Lot T50403 on January 14, 1999
Synercid Lot T50303 on January 7, 1999
Synercid Lot T50705 on January 7, 1999
Synercid Lot CB06556 on January 7, 1999
Synercid Lot T51006 on January 6, 1999
Synercid Lot T50503 on January 6, 1999
Synercid Lot T50906 on January 6, 1999
Synercid Lot CB06557 on December 15, 1998
Synercid Lot CB06558 on December 15, 1998

Documentation for each lot for additional LAL testing and stability testing was also submitted.

Since third party review of these Synercid batches shows compliance with cGMPs, we believe the quality of these batches is established. RPR therefore requests that the Agency re-evaluate whether these batches of Synercid drug product (all batches manufactured and/or distributed after January 28, 1997) may be used to restart the clinical trials immediately (thereby lifting the clinical hold on these Lots) and/or for launch supplies once the Product is approved. If the Division has remaining concerns not addressed by the independent third party review and our quality verification, RPR will respond to any specific points. RPR requests that the Agency provide a written response to this request. Thank you.

Kind regards,

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

Attachment

RHÔNE-POULENC RORER

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

April 27, 1999

FDA
Dockets Management Branch
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

Re: FDA Docket No. 98N-0339

This communication confirms that establishment of the interpretive criteria for the in vitro susceptibility testing of RPR's anti-infective products, Synercid® was conducted by Dr. Albert Sheldon and his team of microbiology reviewers in a timely and efficient fashion with a transparency of the rationales supporting the agency's decisions, an openness to receive sponsor input, a close consideration of the scientific influence of the National Committee for Clinical Laboratory Standards (NCCLS) recommendations on clinical microbiology laboratories and the ongoing work of the agency and a strict attention to the need for audit trails. In addition, Drs. Sheldon, Utrupp, and Roberts provide solid technical support at the NCCLS Subcommittee Meetings for Antimicrobial Susceptibility Testing and promptly initiate action items, as needed, to help ensure consistency of FDA and NCCLS breakpoints, wherever possible.

Sincerely,

/S/
Harriette Nadler, Ph.D., Director, Anti-Infective Clinical Research/Clinical Microbiology

/S/
George Talbot, M.D., Sr. Director, Anti-Infective Clinical Research

/S/
Jack Savarese, M.D., Sr. Director, Anti-Infective Regulatory Affairs

/S/ 4.27.99
Philippe Prokocimer, M.D., Vice President, Anti-Infective & Respiratory Clinical Research

cc: FDA
A. Sheldon
R. Roberts
L. Utrupp
F. Marsik
A. Rakowski
P. Dionne
N. Modelena

RPR
P. Prokocimer
P. Chaikin
M. Talbott
T. Joslin
J. Kerrigan
R. Livesay
B. Lavin
M. Dowzicky
I. Brumpt
L. Normand
C. Feger

Rhône-Poulenc Rorer Pharmaceuticals Inc.
Regulatory Affairs

RECORD OF FDA CONTACT

Date of Contact: May 12, 1999 **Name:** J. Savarese

Issue Date: May 20, 1999 **Signature:** On File

Product: Synercid **Application No:** NDA 50-748 and NDA 50-747

Initiated by: FDA **Made via:** Face-to-Face Meeting at FDA

Division: Anti-Infective Drug Products

Subject: Synercid Labeling and CMC

FDA Attendees:
Sousan Altaire (Clinical Microbiology), Erica Brittain (Statistics), Gary Chikami (Division Director), Sandra Kweder (Acting Office Director), Alexander Rakowsky (Medical TL), Ken Seethater (Pharmaclogist), Albert T. Sheldon (Microbiology TL), JoAnn Spearman (DDMAC Regulatory Review Officer), Patricia Kuker Staub (DDMAC - Reg Counsel/Review), He Sun (Clinical Pharmacology), Susan Thompson (Medical Officer), Jim Timper (Chemist HFD-520)

RPR Attendees:
Kristine Agar (Regulatory Affairs/MPP), Thomas Deets (Regulatory Affairs - Labeling), Michael Dowzicky (Clinical Microbiology), Robert Livesay (Marketing), John Savarese (Regulatory Affairs - Liaison), George Talbot (Clinical Research), Ray Zhu (Biostatistics)

Summary:

Package Insert

RPR submitted a response on May 10 to FDA's most recent wording of the Synercid package insert. This response was the subject of a meeting with the Division of Anti-Infective Drug Products to finalize the package insert. The following agreements were reached regarding each of the points in that May 10th document:

1. Regarding Subpart H information within the box, FDA agreed to RPR's language but will add "on traditional clinical end points" after the word benefit in the sentence that reads "However, a study to verify the clinical benefit of therapy with Synercid is presently underway."

2. Regarding the discussion of bactericidal activity of Synercid in the microbiology section, FDA understood that RPR did accept FDA's language, but commented further that as additional information becomes available, the label can be revised.

3. In the Indications And Usage section, the same change will be made as was for the Subpart H boxed information.

4. Regarding the display of adverse events, FDA proposed a table which would give the lab parameter followed by the critical value, either increase or decrease, followed by the percentage of patients for both Synercid and for the comparator. The Division asked that this be done for all values for which there was a greater than 0.1% incidence. The Agency requested that RPR complete this table and fax these results to them for their review.

5. The Division accepted the display of arthralgia and myalgia proposed by RPR. RPR indicated that some minor adjustment of the numbers was necessary following a validation of the data. FDA agreed to these changes.

6. In the Clinical Studies section:

   a) The Division rejected RPR's revision to include a range of [redacted] percent. The Division indicated that [redacted] percent was FDA's calculation and that traditionally FDA included their values in product labeling. At that point, RPR proposed an alternative plan which would use the FDA numbers, but give the overall number of patients and efficacy rates for the specific infection types. The Agency agreed to this and after considerable discussion, the actual language was agreed upon. The Division will prepare this rewritten section and fax it to RPR within a day or two.

   b) The FDA did agree to the addition of "since these infections were assumed to include gram negative and anaerobic organisms" to FDA's reasons for exclusion from evaluability for patients with lower extremity infections and diabetes or peripheral vascular disease.

   c) RPR had suggested that the statement "none of these differences were statistically significant" be added to the efficacy results for post-operative infections within the Skin and Skin Structure Infection Indication. The Division rejected this since they felt that it implied that these differences which were [redacted] percent efficacy for Synercid and [redacted] percent for comparator will be

considered as actually equivalent by the reader. However, both RPR and the Division agreed that due to the small number of patients that the absolute point value may, in fact, not be different. FDA did agree to add wording to the effect that due to the small number of patients, statistical conclusions could not be reached. RPR agreed with this.

Other Issues

1. The Division was informed that the inspection of the [redacted] has been postponed by approximately one month from mid-May to mid-June. They were also informed that the exact time frame for completion of the inspection for Synercid has not yet been determined, but that overall the effect will be a delay in approval of the [redacted]. The Division commented that they had received the IND amendment regarding Catalytica and that that review was underway and they anticipate a response to RPR regarding the lifting of the clinical hold as requested in the IND amendment for resumption of clinical trials by the end of next week.

2. The Division asked if any promotional materials have been readied for submission to DDMAC. RPR responded that now that the labeling has been completed that promotional material will be readied. Since the approval will be delayed pending clearance of the manufacturing facilities, there will be adequate time for preapproval clearance of the promotional clearance as required under Subpart H approval.

3. The Division commented that in the approval letter there will be mention of the need to pursue the pediatric studies according to recent FDA pediatric initiatives. The Division was informed by RPR that a pediatric development program is currently under discussion and proposals will be submitted to the Agency in the near future. FDA emphasized the need to evaluate the less than 2 years old population for which a potential effect of Synercid on hepatic development might be an issue.

DISTRIBUTION

[redacted]

ORIGINAL

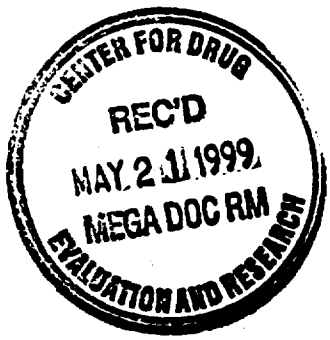
RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

ORIG AMENDMENT

20 May, 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 20850

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

Dear Dr. Chikami:

Attached are RPR's proposed revisions for the label as discussed with FDA at the 12 May, 1999 final label review meeting.

Attachment A is an updated Arthralgia/Myalgia table for the Adverse Events section.

Attachment B is an updated text and table of laboratory values for patients in the comparative trials exhibiting values above or below clinically relevant "critical" values (with an incidence of 0.1% or greater).

RPR received the FDA fax dated 12 May, 1999 with the revised language for the Clinical Studies VREF subsection. RPR proposes minor edits to the text as explained in **Attachment C.**

Attachment D contains RPR's minutes of the 12 May, 1999 meeting and details other changes for the final labeling as agreed by FDA.

RPR will await receipt of the final labeling from FDA incorporating all the changes. A copy of the final labeling on diskette would be greatly appreciated. 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
Senior Director, Regulatory Affairs

JJS/MEE/mee
attachments

k:anti_inf\synercid\ndacorsp\lab20may.doc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Rhone-Poulenc Rorer
Attention: John J. Savarese, M.D., Ph.D.
Senior Director, Regulatory Affairs
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

MAY 24 1999

Dear Dr. Savarese:

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

We also refer to your amendment dated April 30, 1999, received May 4, 1999, serial #477 which provided a response to our August 7, 1998, letter which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues. Specifically, this IND was placed on clinical hold because the manufacturing facility [redacted] which produces the drug product was found to be operating out of Current Good Manufacturing Processes (CGMPs).

Your submission provides for an alternate manufacturing facility, Catalytica Pharmaceuticals, Inc., Greenville, NC.

We have completed the review of your submission and have concluded that clinical trials conducted under this IND may be resumed with drug manufactured at the Catalytica Pharmaceuticals, Inc., facility.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
Attention: Division Document Room
9201 Corporate Boulevard, HFD-520
Rockville, MD 20850

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

Sincerely yours.

/S/

Gary K. Chikami 5/24/99
Director
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
HFD-520/DivFile
HFD-520/PMgr/DillonParker
HFD-520/MO/Rakowsky 5/24/99
HFD-520/MO/Thompson
HFD-520/Clin/Bostwick
HFD-520/Chem/Timper/rd init 5/20/99 5/24/99
HFD-520/Pharm/Seethaler
HFD-520/Micro/Altaie
HFD-520/Stat/Brittain
HFD-520/Biopharm/Pelsor

Concurrence:
HFD-520/CPMS/Bona/rd init 5/19/99 5/24/99
HFD-520/TLChem/Katague/rd init 5/20/99 5/24/99
HFD-520/TLMO/Rakowsky/rd init 5/20/99 5/24/99

REMOVE HOLD (RH)

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

COPY FOR YOUR INFORMATION

May 25, 1999

Gary K. 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

RE: Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
GENERAL CORRESPONDENCE:
Chemistry, Manufacturing and Controls

Dear Dr. Chikami:

Reference is made to our letter of December 18, 1998 and the telephone conversation between FDA and RPR on February 3, 1999, regarding the requirements for the addition of an alternate manufacturing site for the drug product at Catalytica Pharmaceuticals, Inc., Greenville, NC.

RPR wishes to advise the agency that the NDA amendment will be filed in early June (targeted for June 8). In accordance with the agreements made on February 3, the amendment will include 3 months accelerated stability data from a 6 month study, 3 months non-stressed stability data, a statistical evaluation of the stability data, and the CMC microbiological validation package. RPR confirms that Catalytica is ready for a pre-Approval Inspection. As agreed with the Agency, the amendment will be filed requesting expedited review.

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
INFORMATIONAL AMENDMENT:
Chemistry, Manufacturing and Controls
May 25, 1999

[redacted]

We would like to stress that all release and stability testing to date generated at Catalytica, which will be presented in the amendment, have been well within specification.[redacted]

If you would like to discuss this issue further, please contact the undersigned at (610) 454-2636 or Donald Esherick, Senior Manager, Regulatory Affairs CMC Liaison, at (610) 454-5757.

Kind regards,

Rhône-Poulenc Rorer Pharmaceuticals, Inc.

Liuda Shtohryn

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

cc: James Timper, Chemistry Reviewer
David Katague, Ph.D., Team Leader, Chemistry
John J. Savarese, M.D., Ph.D., Senior Director, Regulatory Affairs

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

CMC AMENDMENT

BZ

26 May 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 20850

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747
General Correspondence (Synercid VREF Confirmatory Protocol #396 - amendment #1)

Dear Dr.Chikami:

In reference to the VREF Confirmatory Protocol #396 and teleconferences with FDA on 25 February and 28 April, 1999 attached is the Synercid VREF Confirmatory Protocol #396, amendment #1.

Pursuant to agreements reached during the 25 February, 1999 teleconference, the study has started.

Based on the 28 April, 1999 teleconference, RPR is providing amendment #1 to you for review and prior to finalization. Pharmacokinetic information has been added to this amendment and has not been previously reviewed (Sections 1.3, 2.0, 3.1.1, 5.2.2, 7.3, 7.3.1, 7.3.2, 9.5.1, 9.5.1.1, 9.5.1.2, 9.5.1.3, 9.5.1.4, 9.5.1.5, 9.5.1.6. and 9.5.2). In addition, RPR's proposal for the negative stopping rules is specified in Appendix IV. The positive stopping rules were agreed during the 28 April, 1999 teleconference.

D. Lin and R. Zhu (RPR) proposed to schedule a teleconference to review and finalize the negative stopping rules during the week of 1 June, 1999 (2, 3 or 4 June). M. Elicone will contact M. Dillon Parker to schedule this meeting.

We look forward to receiving any additional comments and plan to finalize the amendment by mid-June as agreed.

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

Sincerely yours,

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

DUPLICATE

K:\ano_in\synercid\ndacorsp\1999\cr096c.doc

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
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Tel 610-454-8000

Rec'd 6/7/99

June 4, 1999

Gary K. 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 20850

RE: Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
NDA Amendment:
Chemistry, Manufacturing and Controls

EXPEDITED REVIEW REQUESTED

Dear Dr. Chikami:

Reference is made to our pending new drug application, to our letter of December 18, 1998 and the telephone conversation between FDA and RPR on February 3, 1999, regarding the requirements for the addition of an alternate manufacturing site for the drug product at Catalytica Pharmaceuticals, Inc., Greenville, NC.

In accordance with the agreements made on February 3, the enclosed amendment includes 3 months accelerated stability data from a 6 month study, 3 months non-stressed stability data, a statistical evaluation of the stability data, and the CMC microbiological validation package. RPR confirms that Catalytica is ready for a pre-Approval Inspection. RPR requests an expedited reivew of this amendment, as agreed in the February 3 teleconference.

If you have any question regarding this amendment, please contact the undersigned at (610) 454-5471 or Donald Esherick, Senior Manager, Regulatory Affairs CMC Liaison, at (610) 454-5757.

Kind regards,

Rhône-Poulenc Rorer Pharmaceuticals, Inc.

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

RHÔNE-POULENC

N-49,5 (PC)

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

ORIGINAL

7 June, 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 20850

Synercid® I.V. (quinupristin and dalfopristin for injection)
[redacted]
Protocol Amendment - Study #143

Dear Dr. Chikami:

Attached is a protocol amendment for study #143 (*An Open Phase I Study of the Pharmacokinetics and Tolerability of RP59500 (quinupristin/dalfopristin) Administered as Repeated 7.5 mg/kg IV Doses to Patient Volunteers with Moderate or Severe Chronic Renal Failure*).

The amendment was required because RPR discovered that the pH of the blood samples obtained from one of the two clinical sites was significantly higher than the other and could have substantially affected the bioanalytical results. This amendment allows for the replacement of all 12 subjects at the affected site.

A copy of this report is also being submitted [redacted]

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
Senior Director, Regulatory Affairs

JJS/MEE/mee
Attachment

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RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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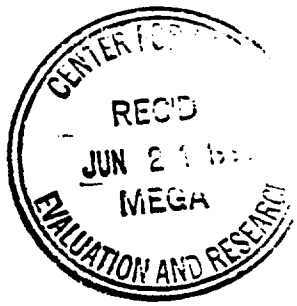
Tel 610-454-8000

18 June, 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 20850

NEW CORRESP
NC



Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-748 (memo and attachment) and
NDA 50-747 (memo only)
Draft Introductory Promotional Material

Dear Dr. Chikami:

Reference is made to NDAs 50-747 and 50-748 and the approvable letters received from FDA on 5 March, 1998 and 4 September, 1998, respectively. Attached is one copy of the draft introductory promotional material for your review. These materials were prepared based upon the approved labeling (FDA provided verbal approval for the final labeling on 7 June, 1999) which was discussed at the 12 May, 1999 meeting with the Division and then updated with a submission dated 20 May, 1999.

Two copies of the draft promotional material have been submitted directly to the Division of Drug Marketing, Advertising and Communications (Ms. Jo Ann Spearmon) for review.

This is the first of five (5) waves of draft introductory promotional materials which will be submitted for pre-clearance.

If you require any additional information, please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

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

JJS/MEE/mee
att

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RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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PO Box 1200
Collegeville, PA 19426-0107
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21 June, 1999

NEW CORRESP
NC

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 20850

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-748 (memo and attachments) and
NDA 50-747 (memo only)
Phase IV Commitment - Pediatric Development

Dear Dr. Chikami:

Below please find RPR's proposed plan to address the following Phase IV commitment as described in the approvable letters for Synercid® (quinupristin/dalfopristin for injection) IV dated 5 March, 1998 and 4 September, 1998, for our new drug applications 50-747 and 50-748, respectively.

> **Excerpt from NDA 50-747 approvable letter:**
> We request that you conduct the following Phase 4 studies..."Studies to obtain pharmacokinetic, safety and efficacy data in the pediatric population (0-16 years of age)."
>
> **Excerpt from NDA 50-748 approvable letter:**
> Commit to conduct: "Studies in pediatric patients to obtain information on the appropriate use of Synercid in the pediatric population (e.g. pharmacokinetic, pharmacodynamic, safety data)."

DUPLICATE

RPR proposes a plan including two elements.

First, we intend to conduct a population pharmacokinetic study in pediatric patients. Because of the venous tolerance of Synercid, RPR considers classical Phase I studies in the pediatric population not to be feasible. A population pharmacokinetic study (#324) will be conducted in 75 patients. The primary objective of this study is a pharmacokinetic assessment. Secondary objectives include safety and efficacy assessments.
The draft #324 Protocol Synopsis is provided in Attachment A.

Second, all available experience with Synercid from pediatric patients enrolled in the

Emergency-use program will be collected and summarized. Data collected from approximately 150 pediatric patients (including those already submitted in the original NDA) treated in the Emergency-use program will be collected and summarized. The objective is to provide these data as supportive information regarding safety and efficacy.

Assuming the positive outcome of the study data, RPR proposes to augment the current labeling to represent the pediatric data in the Indications, Precautions and Pediatric Use sections.

We would appreciate receiving your initial comments on this submission prior to generating a draft written request for pediatric exclusivity.

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
Senior Director, Regulatory Affairs

Attachment
JJS/MEE/mee

ORIGINAL

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
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DRUG AMENDMENT

July 8,1999

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 20850

Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747
Protocol Amendment

Synercid VREF Confirmatory Protocol #396 - Amendment #1 and Revised Protocol)

Dear Dr.Chikami:

In reference to the VREF Confirmatory Protocol #396 and pursuant to agreements reached with FDA on 25 February, 28 April, and 24 June, 1999, attached is the Synercid VREF Confirmatory Protocol #396, amendment #1 and revised protocol.

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

Sincerely yours,

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

JJS/MEE/nrf
Attachment

DUPLICATE

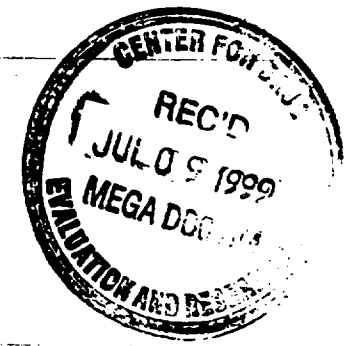
RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

(V-487)
PN

July 8, 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 20850

[redacted]

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

Serial #487
Phase IV Commitment
Protocol for Synercid Study #159 [redacted]

Dear Dr. Chikami:

Attached is the final protocol for Synercid Study #159 ("A Phase I, Open Randomized Parallel Group Pharmacokinetic and Safety Study of the Interaction Between Repeated Administration of [redacted]

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

cc (memo only) [redacted] NDA 50-747 and NDA 50-748

Sincerely yours,

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

JJS/MEE/mee
Attachment

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DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD-520
dillon-Parker

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JUL 21 1999

Kristine M. Agar
Manager
Marketed Product Practices
Worldwide Regulatory Affairs
Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

RE: NDA # 50-747/50-748
Synercid I.V.
(quinupristin/dalfopristin for injection)
MACMIS ID # 8053

Dear Ms. Agar:

Reference is made to Rhone-Poulenc Rorer Pharmaceuticals Inc.'s (RPR) June 18, 1999, letter requesting comments on proposed promotional launch materials for Synercid IV (Synercid). These materials included an introductory physician fax, an introductory pharmacist fax, a dosage card, a wholesale sheet, and a survey sell sheet.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the submission and offers the following comments. DDMAC's comments regarding a specific claim or presentation should be applied to all similar claims or presentations throughout all current and future promotional materials.

General Comments

The general theme or focus of the proposed launch submission is that Synercid is a major breakthrough in treating gram (+) resistant pathogens. For example, presentations of bolded headers that state "A focused assault on gram-positive resistance," and "Announcing a major breakthrough against resistant gram-positive pathogens," emphasize this theme. These statements and presentations would be misleading because they imply a greater efficacy for Synercid than supported by substantial clinical evidence.

Specifically, the statements imply that Synercid has utility in treating all resistant gram-positive pathogens, which is not the case. Synercid is approved for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterocccus faecium* (*VREF*) bacteremia. DDMAC would not object to a presentation that discusses Synercid as a major breakthrough for VREF only.

Synercid's indication to treat bacteremia caused by VREF was approved under FDA's accelerated approval regulations based upon a demonstrated effect on a surrogate endpoint that is likely to predict clinical benefit. DDMAC notes that RPR presents the information about the limitation associated with this indication on the first page of the physician and pharmacist fax. RPR also presents the VREF indication on the second page of the fax, combined with a traditionally approved indication, e.g., complicated skin and skin structure infections. The presentation on the second page of the fax that is in bolded type is given greater emphasis than the limiting information regarding Synercid's use in treating bacteremia caused by VREF that is presented on the first page of the fax. Therefore, DDMAC recommends that RPR revise the general theme of the promotional materials and the presentation of Synercid's indication, including the limiting information, to treat bacteremia caused by VREF.

DDMAC has the following additional comments:

Introductory Physician Fax

- **"Synercid is generally well tolerated..."**

  The above statement would be misleading because it minimizes the extent to which patients experienced adverse events associated with the use of Synercid. In the clinical studies used as the basis of approval, the incidence of adverse events associated with the use of Synercid were inflammation at infusion site (42%), pain at infusion site (40%), and edema at infusion site (17%), etc. These rates would not be commensurate with the statement that Synercid is "generally well tolerated." Additionally, approximately 23% of patients discontinued therapy due to drug related adverse events. Therefore, DDMAC recommends that RPR delete the phrase "generally well tolerated."

- **"No dosage adjustment is required in patients with renal impairment or in patients undergoing hemodialysis or peritoneal dialysis, in elderly patients, or children."**

  The physician fax would be misleading because it fails to reveal facts material regarding the use of Synercid in children. Specifically, the fax fails to include the information that the safety and effectiveness of Synercid in patients under 16 years of age have not been established. DDMAC notes that RPR references the

above statement with a footnote that states, "Based on a limited number of patients less than 16 years of age treated with 7.5mg/kg under emergency-use conditions." However, this footnote is insufficient to balance the predominant message that no dosage adjustment is required in specific patient populations, of which children are included. Additionally, footnotes are not considered to be an appropriate medium to convey important information that provides context for a claim. Therefore, DDMAC recommends that RPR revise the fax to include the information regarding the safety and effectiveness of Synercid's use in children less than 16 years of age and increase the prominence and readability of the information currently presented as a footnote.

- **"Synercid...offers standardized dosing regardless of renal impairment..."**

Because Synercid is primarily cleared hepatically, DDMAC recommends that RPR include the following information to balance the above presentation:

- Pharmacokinetic data in patients with hepatic cirrhosis (Child Pugh A or B) suggests that dosage reduction may be necessary, but exact recommendations cannot be made at this time.

- **Risk Information**

DDMAC notes that RPR presents the incidence of arthralgia and myalgia in the physician fax. However, the presentation does not convey the fact that these adverse events may be severe, as stated in the Precaution section of the approved product labeling (PI). Additionally, DDMAC notes that RPR includes this information in the pharmacist fax. Therefore, DDMAC recommends that RPR revise the presentation of risk information to include the above information.

DDMAC also recommends that RPR include the incidence of nausea (e.g., 3.8%, 2.8%, and 4.9%) in the presentation of risk information. DDMAC makes this recommendation so that practitioners will know that gastrointestinal adverse events are also associated with the use of Synercid.

- **Drug Interactions**

According to the PI, Synercid significantly inhibits cytochrome P450 3A4 metabolism of cyclosporine A, midazolam, nifedipine[redacted] Additionally, cyclosporine therapeutic levels should be monitored when cyclosporine must be used concomitantly with Synercid, and not whenever possible, as stated in the promotional piece. Therefore, DDMAC recommends that RPR include the above referenced drugs to balance the presentation of

information regarding drug interactions. DDMAC also recommends that RPR revise the information regarding cyclosporine monitoring.

- **"Much has been heard about the mounting problem of resistant gram-positive infections. Now, learn more about a focused solution-Synercid."**

The above statement would be misleading because it implies a greater efficacy for Synercid than supported by substantial evidence. Specifically, the statements imply efficacy for Synercid against all resistant gram-positive infections, which is not the case. Synercid is indicated to treat bacteremia caused by one resistant gram-positive pathogen, VREF. Additionally, Synercid's approval to treat VREF is based on a surrogate endpoint and not on the results from well-controlled clinical studies. The phrase "a focused solution" implies a clinical benefit that has not been substantiated. Therefore, it would be misleading to imply that Synercid has activity against other resistant gram-positive pathogens or to refer to Synercid as a "focused solution." DDMAC recommends that RPR revise the above presentation and delete the phrase "a focused solution."

Introductory Pharmacy Fax

DDMAC refers RPR to the introductory physician fax section for our comments regarding similar claims and presentations in the introductory pharmacy fax. DDMAC has these additional comments.

Indication

DDMAC notes that RPR includes the information from the PI that Synercid is not active against *Enterocccus faecalis* in the introductory physician fax. However, this information is conspicuously absent in the introductory pharmacist fax. This is important information regarding limitations on the use of this product. Therefore, DDMAC recommends that RPR revise the introductory pharmacist fax to include this information.

Reconstitution

To balance the presentation of information regarding the reconstitution of Synercid, DDMAC recommends that RPR include the information that Synercid should not be diluted with saline solutions because it is not compatible with these agents. This information is bolded in the section of the PI that discusses Synercid's compatibility with other agents.

Dosage Card

DDMAC refers RPR to our comments in the general comments and in the introductory physician and pharmacists fax sections regarding similar claims and presentations found in the dosage card. DDMAC has the following additional comments:

The dosing card contains a presentation of abnormal laboratory values associated with the use of Synercid. DDMAC notes that RPR selectively presents the abnormal laboratory values listed as "Other" in the PI, but fails to include the most frequently observed abnormalities in laboratory studies associated with the use of Synercid, thus, making this presentation misleading. The most frequently observed abnormalities in laboratory studies were in total and conjugated bilirubin. Therefore, DDMAC recommends that the presentation of abnormal laboratory values be revised to include this information.

Wholesale Sheet

DDMAC refers RPR to the introductory pharmacist fax section for our comments regarding reconstituting Synercid with saline solutions. DDMAC has no further comments at this time.

Survey Sell Sheet

DDMAC refers RPR to the introductory pharmacist fax section for our comments regarding reconstituting Synercid with saline solutions. DDMAC has no further comments at this time.

If RPR has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

DDMAC reminds RPR that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8053 in addition to the NDA number.

Sincerely,

/S/

Jo Ann Spearmon, Pharm.D., M.P.A.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

RHÔNE-POULENC

Rhône-Poulenc Rorer

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

July 23, 1999

Gary K. 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 20850

RE: Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
NDA Amendment:
Chemistry, Manufacturing and Controls
Six Month Stability Update from Catalytica

EXPEDITED REVIEW REQUESTED

Dear Dr. Chikami:

Reference is made to our pending new drug application, to our letter of December 18, 1998, to the telephone conversation between FDA and RPR on February 3, 1999, regarding the requirements for the addition of Catalytica Pharmaceuticals, Inc., Greenville, NC as a manufacturing site for the drug product and to the amendment filed on June 4.

Enclosed please find the 6 months accelerated stability data, 6 months non-stressed stability data, and a statistical evaluation of the stability data from Catalytica. The 6 month data from Catalytica is similar to the data generated from lots manufactured at [redacted]. As discussed and agreed upon in our February 3 telephone conversation, a 24 month shelf-life is requested for Synercid manufactured at Catalytica when stored at refrigerated conditions (2° - 8°C).

In addition, per a request from Mr. James Timper, the Reviewing Chemist, three certificates of analysis issued by RPR France for the clinical batches recently manufactured at Catalytica are enclosed. The data from RPR France confirm the data generated by Catalytica included in the June 4 amendment and demonstrate that the optimization of the siliconization process has substantially reduced the particulate matter levels in the drug product.

Finally, with the completion of registration requirements for Catalytica and the scheduling of the Pre-Approval Inspection at Catalytica for August 30 through September 3, RPR hereby withdraws [redacted] from the NDA as a manufacturer of the drug product, without prejudice to refiling in the future. Therefore, RPR requests approval only for Catalytica Pharmaceuticals, Inc., to manufacture Synercid (quinupristin/dalfopristin) I.V. drug product.

If you have any questions regarding this amendment, please contact the undersigned at (610) 454-5471 or Donald Esherick, Senior Manager, Regulatory Affairs CMC Liaison, at (610) 454-5757.

Kind regards,

Rhône-Poulenc Rorer Pharmaceuticals, Inc.

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

[redacted]

RHÔNE-POULENC

Rhône-Poulenc Rorer Pharmaceuticals Inc.

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

July 28, 1999

Gary K. 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 20850

RE: Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
NDA Amendment: Chemistry, Manufacturing and Controls
Six Month Stability Update from Catalytica

Dear Dr. Chikami:

Reference is made to our pending new drug application, to our letter of December 18, 1998, to the telephone conversation between FDA and RPR on February 3, 1999, regarding the requirements for the addition of Catalytica Pharmaceuticals, Inc., Greenville, NC as a manufacturing site for the drug product, and to the amendments filed on June 4 and July 23, 1999.

In the amendment filed on July 23, 1999, which contained the 6 months accelerated stability data, 6 months non-stressed stability data, and a statistical evaluation of the stability data from Catalytica, one page of the stability report was missing. This page contains stability data for Batch 8L3015 stored at +5°C, and is provided herewith. This is page 17 of Report RPR/RD/CPD/PQA n°8311, which becomes page 19a of the amendment filed on July 23.

We apologize for any inconvenience this may have caused in your review of this amendment. If you have any questions, please contact the undersigned at (610) 454-5471 or Donald Esherick, Senior Manager, Regulatory Affairs CMC Liaison, at (610) 454-5757.

Kind regards,

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

RHÔNE-POULENC

Rhône-Poulenc Rorer *Research and Development*

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107

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

Tel 610-454-5618
Fax 610-454-5289

August 2, 1999

Murray M. Lumpkin, M.D.
Deputy Center Director
CDER, HFD-3
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Mac,

I just wanted to give you a "heads up" to the Synercid approval that we just received from the U.K. Medicines Control Agency (see attached). The U.K. is our Reference Member State for the soon-to-begin European Mutual Recognition Procedure. As that review progresses, I will keep you updated. By way of U.S. activity, I am very proud of the progress that the RPR and FDA teams have made on bringing the NDA to approval!

We have been working with the FDA Review Division and the Atlanta District Office to have a Preapproval Inspection of the Catalytica manufacturing facility August 30 to September 2. The inspector has agreed to fax his inspection results to the Division Reviewing Chemist (Dr. Timper) immediately on completion of the inspection so that the Chemist's Review can be completed. Given that the Reviewing Division has cooperated with us to resolve all of the remaining approval issues, we would hope that final NDA approval could be granted by September 15.

Realizing this target date is crucial for two reasons: 1) it coincides with the initiation of the various Mutual Recognition Procedure reviews being conducted on Synercid across Europe. An FDA approval, just as these reviews begin, would be an extremely positive note upon which to inaugurate this crucial regulatory undertaking; 2) ICAC begins September 26 and this pivotal scientific meeting presents an opportunity to demonstrate how FDA and RPR have positively interacted to bring an important therapeutic breakthrough to the market. If we are able to gain approval by the fifteenth, we will be able to focus on the FDA's Synercid approval at the ICAC meeting.

Murry M. Lumpkin
August 2, 1999
Page 2

I will try to get in touch with you this week for a 5-minute chat to see if there is anything additional that I can do to ensure a mid-September Synercid approval. Again, I want to emphasize how much RPR and I appreciate the fine scientifc and medical expertise that the FDA staff has displayed during the development and approval of this product!

I look forward to talking to you soon.

Best regards,

Max W. Talbott, Ph.D.

MWT/ae
Attachment

MEDICINES CONTROL AGENCY

THE MEDICINES FOR HUMAN USE (MARKETING AUTHORISATIONS ETC.) REGULATIONS SI 1994 No.3144

GRANT OF MARKETING AUTHORISATION

MARKETING AUTHORISATION NO: PL 00012/0328
AUTHORISED NAME:
Synercid

Granted to:
MAY & BAKER LIMITED
Trading as RHONE POULENC RORER
RPR HOUSE
50 KINGS HILL AVENUE
WEST MALLING
KENT
ME19 4AH
UNITED KINGDOM

This Marketing Authorisation, under the above reference number is hereby granted in respect of the product. The particulars of the product are set out in the attached document and is subject to the further provisions set out or referred to in the Schedule.

This Marketing Authorisation, as now granted, unless previously revoked will continue in force until the expiry date given below.

Date of Grant: 29/07/1999
Date of Expiry: 28/07/2004

MRS KEELY KENNEDY
A person authorised to sign on behalf of the Secretary of State for Health

DEPARTMENT OF HEALTH

Department of Health
MEDICINES CONTROL AGENCY
Market Towers 1 Nine Elms Lane London SW8 5NQ

Telephone 0171 273-0314
Fax 0171 273-0195

MAY & BAKER LIMITED
RPR HOUSE
50 KINGS HILL AVENUE
WEST MALLING
KENT
ME19 4AH
UNITED KINGDOM

30/07/1999

Dear Sir/Madam,

THE MEDICINES FOR HUMAN USE (MARKETING AUTHORISATIONS ETC.) REGULATIONS 1994

I refer to your application received on 26/09/1997. This application has been taken to include any replacement pages for pages of the application which were originally submitted by you and any amendments to the application which were made pursuant to your written request.

Authority has been given for the grant of a marketing authorisation for:

Marketing Authorisation: PL 00012/0328
Product:
Synercid

The formal document is enclosed together with the details from your application. These constitute the particulars of the authorisation. If you consider them to contain information which is incorrect or is not in accordance with the amendments, please return it immediately indicating any errors.

In relation to the above authorisation you will wish to note and consider the following:

1) The authorisation is subject to standard provisions which are contained in the schedule to the authorisation.

2) Your attention is drawn to the requirements concerning the reporting of suspected adverse reactions under the part(2) of section 7 to the Medicines for Human Use (Marketing Authorisations Etc) Regulation 1994.

3) It has been recommended that in the UK, this product should display an inverted black triangle on product information, loose data sheets, MIMS, the BNF and in any promotional material, although this does not relate to company reporting requirements.
The black triangle status will be reviewed after two years. In the meantime it is important that you advise Miss Kate Foy (Room 1014) of the date on which the product is introduced on the market.

Yours faithfully,

MRS KEELY KENNEDY

PL 00012/0328

LICENCE DETAILS

Route of Administration: INTRAVENOUS

Package Details:

Package Number: 1

Package Size:

Container:
VIAL

Closure:
CAP

Shelf Life Details:
5 HOURS Reconstituted
24 MONTHS Unopened

Storage Conditions:
Unopened vials should be stored under refrigeration (2 to 8°C). The infusion solution should not be frozen.

Company Names and Functions:

Name:
CATALYTICA PHARMACEUTICALS INC
PO BOX 1887, CORNER OF US13/NC11 & HWY US264
GREENVILLE, NORTH CAROLINA 27835-1887
UNITED STATES OF AMERICA
Function:
ASSEMBLER (PACKAGER)
MANUFACTURER - PRODUCT
QC SITE

Name:
RHONE-POULENC RORER
AVDA. LEGANES NO. 13
28925 ALCORCON
SPAIN
Function:
ASSEMBLER (PACKAGER)
BATCH RELEASE SITE

Name:
RHONE-POULENC RORER
35 AVENUE JEAN JAURES
92395 VILLENEURE LA GARENNE
FRANCE
Function:
MANUFACTURER - ACTIVE

Name:
RHONE-POULENC RORER LIMITED

SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1. Trade Name of the Medicinal Product

Synercid®

2. Qualitative and Quantitative Composition

Each vial contains 150 mg quinupristin and 350 mg dalfopristin as the mesilate salts.

3. Pharmaceutical Form

Powder for solution for infusion

Clinical Particulars

4.1. Therapeutic Indications

Synercid is indicated for the treatment of the following infections when known or suspected to be caused by susceptible gram-positive organisms, when intravenous therapy is appropriate, and when there are no other antibacterial agents active against the organisms which are suitable for treatment of the infection in the individual patient:

- skin and soft tissue infections
- clinically significant infections due to *E. faecium*

(see Sections 4.4 *Special Warnings and Special Precautions for Use* and 5.1 *Pharmacodynamics*)

- Synercid should be used in combination with an agent(s) active against Gram-negative organisms if a mixed infection is documented or suspected.
- Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and Method of Administration

ORIGINAL

ORIG AMENDMENT

NC

RHÔNE-POULENC

Rhône-Poulenc Rorer

Research and Development

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

17 August, 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 20850

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-748 (memo and attachment) and
NDA 50-747 (memo only)
Draft Introductory Promotional Material

Dear Dr. Chikami:

Reference is made to NDAs 50-747 and 50-748 and the approvable letters received from FDA on 5 March, 1998 and 4 September, 1998, respectively. Attached is a Trade Sales Cover Letter which should have been included with the wave 1 materials that you received on 18 June, 1999.

Two copies of this additional letter have been submitted directly to the Division of Drug Marketing, Advertising and Communications (Ms. Jo Ann Spearmon) for review.

If you require any additional information, please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Sayarese, MD, PhD
Senior Director, Regulatory Affairs

JJS/MEE/mee
att

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ORIGINAL

COPY

RHÔNE-POULENC

ORIG AMENDMENT

AF

Rhône-Poulenc Rorer

Research and Development

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

17 August, 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 20850

Synercid® (quinupristin/dalfopristin) I.V.

NDA 50-748 (memo and attachments) and
NDA 50-747 (memo only)

FINAL PRINTED LABEL - Updated PI

Dear Dr. Chikami:

In anticipation of marketing approval for Synercid and in accordance with 21 CFR §314.105(b), we have enclosed twenty copies of the final printed labeling (for the package insert only) for the Synercid 500 mg vial (quinupristin and dalfopristin) I.V. We had previously submitted twenty copies of this package insert in the submission dated 10 August, 1999; however, we discovered that the "flow" of the text in that package insert was not consistent with our specifications. M. Elicone discussed the finding with M.D. Parker on 16 August, 1999. MDP stated that since there were no differences in text (per agreements reached with FDA), this was not a problem.

Please destroy the 20 copies of the package insert provided to you on 10 August, 1999 and retain these copies since they are representative of those which will be used for the first commercial packages.

RPR would like to have your approval of the package labels as soon as possible so that we may proceed to manufacture launch supplies with confidence.

If you have any questions please do not hesitate to contact me or Ms Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese, M.D., Ph.D.
Senior Director, Reg Affairs

Attachment
JJS/MEE/mee

k:\anb_inf\synercid\1999\ndacorsp\nlpria2.doc

DUPLICATE

N/C

RHÔNE-POULENC

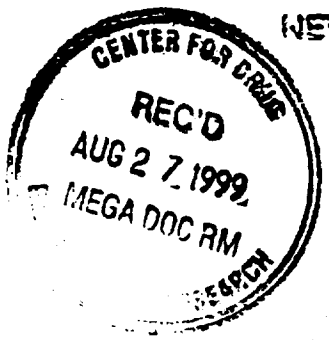
Rhône-Poulenc Rorer

Research and Development

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

26 August, 1999

NEW CORRESP



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 20850

Synercid® I.V. (quinupristin and dalfopristin for injection)
NDA 50-748 (memo and attachment) and
NDA 50-747 (memo only)
Draft Introductory Promotional Material

Dear Dr. Chikami:

Reference is made to NDAs 50-747 and 50-748 and the approvable letters received from FDA on 5 March, 1998 and 4 September, 1998, respectively. Reference is also made to our June 18 and August 17, 1999 submissions of Synercid draft introductory promotional materials.

Two copies of the draft promotional material have been submitted directly to the Division of Drug Marketing, Advertising and Communications (Ms. Jo Ann Spearmon) for review.

This is the second of five (5) waves of draft introductory promotional materials which will be submitted for pre-clearance in accordance with 21 CFR 314.550.

If you require any additional information, please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

Melicone for JJS

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

JJS/MEE/mee
att

k:anti_inf\synercid\ndacorsp\promomt3.doc

RHÔNE-POULENC

Rhône-Poulenc Rorer *Research and Development*

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

2 September, 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 20850

Synercid® (quinupristin/dalfopristin) I.V.

NDA 50-748 (memo and attachments) and
NDA 50-747 (memo only)

Phase IV Commitment - Pediatric Study #324

Dear Dr. Chikami:

In reference to our Phase IV commitment as described in the approvable letters for Synercid® (quinupristin/dalfopristin for injection) IV dated 5 March, 1998 and 4 September, 1998, for our new drug applications 50-747 and 50-748, respectively, our submission dated 21 June, 1999 and our teleconference with FDA on 22 July, 1999, attached is our proposed Pediatric Study protocol #324 (Open-Label, Multicenter, Phase III Study of the Population Pharmacokinetics of IV Synercid (7.5 mg/kg Q8H) in 75 Pediatric Patients).

RPR would appreciate receiving any comments you may have on this protocol. We intend to initiate the study in November, 1999.

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

Sincerely yours,

Melicone for JJS

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

Attachment
JJS/MEE/mee

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

SEP - 2 1999

Kristine M. Agar
Manager
Marketed Product Practices
Worldwide Regulatory Affairs
Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

RE: **NDA # 50-747/50-748**
Synercid I.V.
MACMIS ID #8053

Dear Ms. Agar:

Reference is made to Rhone-Poulenc Rorer Pharmaceuticals Inc.'s (RPR) August 6, 1999, letter responding to the Division of Drug Marketing, Advertising, and Communications' (DDMAC) July 21, 1999, comment letter regarding proposed launch materials for Synercid I.V. (Synercid). Reference is also made to an August 17, 1999, draft trade sales cover letter submitted by RPR for DDMAC's review and comment. RPR stated that the trade sales cover letter will accompany the wholesale sell sheet and the survey sell sheet.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed RPR's response and the revised physician and pharmacist fax and offers the following comments. Comments regarding a specific claim or presentation should be applied to all similar claims or presentations throughout all current and future promotional materials.

General Comments

- **"A Focused Assault On Gram-Positive Resistance"**

  DDMAC notes RPR's stated intention to delete the phrase, "On Gram-Positive Resistance," and revise the above statement to "A Focused Assault." DDMAC has no further comments at this time.

- **"Now FDA Approved"**

DDMAC acknowledges RPR's stated intention to move the above subheader from the front page of the physician and pharmacist fax to the bottom of the last page of these promotional pieces. DDMAC has no further comments at this time.

Indication

DDMAC acknowledges RPR's intention to state the indication, i.e., "For the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia," in conjunction with the accelerated approval information associated with this indication, on the front page of the physician and pharmacist fax. Additionally, DDMAC acknowledges that RPR will unbold the indication text that appears on the second page of the physician and pharmacist fax. DDMAC has no further comments at this time.

- **"Announcing a Major Breakthrough Against Resistant Gram-Positive Pathogens"**

DDMAC acknowledges RPR's stated intention to delete the above headline. DDMAC has no further comments at this time.

Introductory Physician Fax

- **"Synercid is generally well tolerated..."**

DDMAC acknowledges RPR's stated intention to delete the above phrase from all promotional materials. DDMAC has no further comments at this time.

- **"...no dosage adjustment is required in patients with renal impairment or in patients undergoing hemodialysis or peritoneal dialysis, in elderly patients, or children."**

DDMAC notes that RPR proposes to revise the above statement to, "No dosage adjustment is required in elderly patients, and based on a limited number of patients less than 16 years of age treated with 7.5mg/kg under emergency-use conditions, no dosage adjustment is required in children." However, DDMAC objects to RPR's proposed revision. According to the approved product labeling (PI), the safety and effectiveness of Synercid in patients under 16 years of age have not been established. This is important information that needs to be included, especially in presentations that discuss " no dosage adjustment" in specific patient populations. Therefore, DDMAC reiterates its recommendation

that RPR revise the fax to include the information regarding the safety and effectiveness of Synercid's use in children less than 16 years of age.

""Synercid...offers standardized dosing regardless of renal impairment"

DDMAC acknowledges RPR's stated intention to revise the above statement to include the information that patients with hepatic cirrhosis may require a dose adjustment with Synercid therapy. DDMAC has no further comments at this time.

Risk Information

DDMAC acknowledges RPR's stated intention to revise the presentation of risk information in both the introductory physician fax and the introductory pharmacist fax to include the information that episodes of arthralgia and myalgia, some severe, have been reported in patients treated with Synercid. Additionally, RPR will include the incidence of nausea (3.8%, 2.8%, and 4.9%) in the presentation of risk information. DDMAC has no further comments at this time.

Drug Interactions

DDMAC acknowledges RPR's stated intention to revise the drug interaction presentation to "P450 3A4 substrates (e.g. cyclosporine A, midazolam, nifedipine [redacted]) should be used with caution and monitored when coadministered with Synercid. Those drugs used concomitantly that may prolong the QT_c interval should be avoided." DDMAC has no further comments at this time.

"Much has been heard about the mounting problem of resistant gram-positive infections. Now, learn more about a focused solution-Synercid."

DDMAC acknowledges RPR's stated intention to revise the above statements to "To learn more about Synercid, please see the accompanying full prescribing information." DDMAC has no further comments at this time.

Introductory Pharmacy Fax

DDMAC acknowledges RPR's stated intention to apply all revisions made to the introductory physician fax to the introductory pharmacist fax. DDMAC also notes RPR's statement that it inadvertently omitted the statement, "Synercid is not active against *Enterococcus faecalis*," from the introductory pharmacist fax. RPR will revise the fax to include this information. DDMAC has no further comments at this time.

Reconstitution

DDMAC acknowledges RPR's stated intention to include the information that Synercid should not be diluted with saline solutions because it is not compatible with certain agents. DDMAC has no further comments at this time.

Dosage Card

DDMAC acknowledges RPR's statement that the chart on page 3 of the dosage card was extracted from a medical reference text to provide information to physicians regarding basic physiologic disorders often occurring in patients with severe infections, and is not specific to Synercid. DDMAC also notes RPR's stated intention to revise the heading for the chart to "Acid-Base Disturbances and Compensation Occurring in Patients With Severe Infections." DDMAC has no further comments at this time.

"A Focused assault on Gram-positive resistance"

DDMAC acknowledges RPR's stated intention to delete the above headline that appears on the front of the dosing card. DDMAC has no further comments at this time.

Wholesale Sheet

DDMAC acknowledges RPR's stated intention to revise the wholesale sheet to include the information regarding reconstituting Synercid with saline solutions. DDMAC has no further comments at this time.

Survey Sell Sheet

DDMAC acknowledges RPR's stated intention to revise the survey sell sheet to include the information regarding reconstituting Synercid with saline solutions. DDMAC has no further comments at this time.

Trade Sales Cover Letter

DDMAC has reviewed the trade sales cover letter and has no additional comments at this time.

If RPR has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

DDMAC reminds RPR that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8053 in addition to the NDA number.

Sincerely,

JoAnn Spearmon, Pharm.D., M.P.A.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

TO: Jim Timper
Maureen Dillon Parker

DATE: 9/3/99
NDA: 50-747
FEI: 8130-5131/99

FAX: 301-822-2325

Preapproval inspection of NDA 50-747, Synercid 500mg, at Catalytica Pharmaceuticals, Greenville NC found firm ~~Cap~~ re adhering to NDA Commitments and in general Compliance with CGMPs. Minor GMP deviations were noted and the firm promised immediate Correction.

Robert C. Coleman
Investigator
DSID/ARQ-00