CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-747

50-748

MICROBIOLOGY REVIEW

HFD-520/Koch

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

JAN 16 1998

Microbiologist's Review #1 of NDAs 50-748, 50-747
January 16, 1998

A. 1. **APPLICATION NUMBER:** 50-748 and 50-747

APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

2. **PRODUCT NAMES:** Synercid (quinupristin/dalfopristin) I.V.

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 500 mg/vial lyophilized powder (150 mg of quinupristin and 350 mg dalfopristin) in a 10 ml glass vial. Synercid is to be administered intravenously.

4. **METHOD(S) OF STERILIZATION:** [redacted]

5. **PHARMACOLOGICAL CATEGORY:**

NDA 50-748: 1P; indicated for the treatment of complicated skin and skin structure infections[redacted]

NDA 50-747: 6S; indicated for treatment of cases associated with concurrent bacteremia and infections caused by *Staphylococcus aureus* (including [redacted] susceptible and [redacted] resistant strains), in patients failing other therapies including cases associated with concurrent bacteremia.

B. 1. **DATE OF INITIAL SUBMISSION:** September 5, 1997

2. **AMENDMENT:** Amendment (Container/closure integrity) 1/9/1998

3. **RELATED DOCUMENTS:** Facsimile from Don Esherich (11/26/97)

4. **ASSIGNED FOR REVIEW:** October 3, 1997

5. **DATE OF CONSULT REQUEST:** September 16, 1997

C. REMARKS:

The manufacture of the 2 active ingredients in Synercid involves [redacted] Quinupristin and dalfopristin are manufactured by [redacted] The drug product, Synercid, is manufactured and tested by [redacted]

D. CONCLUSIONS:

The submission is recommended for approval on the basis of sterility assurance.

/S/ - 1/16/98
Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 1/16/98

cc:

NDAs 50-748 and 50-747
HFD-520/ Div. File
HFD-805/ Uratani
HFD-520/CSO/Roche
HFD-520/Chemist/ Timper
HFD-520/ Katague
drafted by: Brenda Uratani, 1/16/98
R/D initialed by P. Cooney, 1/16/98

FEB 2 1998

ADDENDUM TO REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Nocto 520

Microbiologist's Review #1 of NDAs 50-748, 50-747
Addendum to Pending Application
February 2, 1998

A. 1. **APPLICATION NUMBER:** 50-748 and 50-747

APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

2. **PRODUCT NAMES:** Synercid (quinupristin/dalfopristin) I.V.

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 500 mg/vial lyophilized powder (150 mg of quinupristin and 350 mg dalfopristin) in a 10 ml glass vial. Synercid is to be administered intravenously.

4. **METHOD(S) OF STERILIZATION:** [redacted]

5. **PHARMACOLOGICAL CATEGORY:**

NDA 50-748: 1P; indicated for the treatment of complicated skin and skin structure infections [redacted]

NDA 50-747: 6S; indicated for treatment of cases associated with concurrent bacteremia and infections caused by *Staphylococcus aureus* (including methicillin-susceptible and [redacted] esistant strains), in patients failing other therapies including cases associated with concurrent bacteremia.

B. 1. **DATE OF INITIAL SUBMISSION:** September 5, 1997

2. **AMENDMENT:** Amendment (Container/closure integrity) 1/9/1998

3. **RELATED DOCUMENTS:** Facsimile from Don Esherich (11/26/97)
483 from Compliance issued 11/24/97

4. **ASSIGNED FOR REVIEW:** October 3, 1997

5. **DATE OF CONSULT REQUEST:** September 16, 1997

C. **REMARKS:**

This addendum is to reverse the recommendation for approval by Microbiologist's Review #1. The Not Approvable conclusion is based on the new information provided by the FDA inspection. The drug product is manufactured at [redacted].

D. **CONCLUSIONS:**

The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "Review Notes".

/S/ 2/2/98
Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 2/2/98

cc:

NDAs 50-748 and 50-747
HFD-520/ Div. File
HFD-805/ Uratani
HFD-520/CSO/Roche
HFD-520/Chemist/ Timper
HFD-520/ Katague
drafted by: Brenda Uratani, 2/2/98
R/D initialed by P. Cooney, 2/2/98

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

CLINICAL MICROBIOLOGY REVIEW

NDA#: 50-747 **REVIEW #1** **REVIEW DATE: 10/7/97**

SUBMISSION TYPE:	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
NDA	9/5/97	9/8/97	9/ 9/97

NAME AND ADDRESS OF APPLICANT:

Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Rd.
Collegeville, PA 19426-0107

CONTACT PERSON:

John J Savarese, MD, Ph.D.
Director, Regulatory Affairs
500 Arcola Rd.
Collegeville, PA. 19426-0107
610-454-5471

DRUG PRODUCT NAME:

Proprietary:	Synercid
Nonproprietary:	Quinupristin/Dalfopristin
Code Names/#'s:	RP59500(RP57669/RP54476)
Chemical Formula(empirical):	Quinupristin = $C_{53}H_{67}N_9O_{10}S$ Dalfopristin = $C_{34}H_{50}N_4O_9$

INDICATIONS: Infections due to vancomycin-resistant *Enterococcus faecium* including cases with concurrent bacteremia

DOSAGE FORM:
STRENGTH:
ROUTE OF ADMINISTRATION: Intravenous

RELATED DOCUMENTS:

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA#: 50-747 **REVIEW #1** **REVIEW DATE: 10/7/97**

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REMARKS/COMMENTS:

The microbiology portion of this application is approvable on the condition that the indicated changes be incorporated into the labeling.

It is, however, noted that this submission lacks details in the following areas which may have helped clarify the data provided and allowed a better assessment of the efficacy and safety of the drug when used in the clinical setting. These areas are: 1) the type and numbers of patients with *Enterococcus faecium* which were available to evaluate in order to ascertain Synercid's efficacy; 2) the lack of pharmacokinetic data on the levels of Synercid that are achievable in the lung tissue of humans; 3) the lack of data on the activity of each of the components of Synercid against bacterial isolates thus not allowing analysis to be done as to whether individual component testing may have been a better way to predict efficacy against *E. faecium*; 4) the lack of epidemiological data relating to the dissemination of vancomycin-resistant *E. faecium* (VRE*faecium*), vancomycin-resistant *E. faecalis* (VRE*faecalis*), Synercid, and Synercid and vancomycin-resistant *E. faecium* and *E. faecalis* in the hospital setting in which Synercid was used despite the fact that the applicant in their submission noted that the potential for the transmission of resistant organisms was a possibility; 5) the lack of animal model and human data on the postantibiotic effect against targeted pathogens; 6) the lack of data relating to the peak concentration of achievable drug to the MIC as it may relate to development of resistant organisms; 7) the lack of in vitro data on the transmissibility of Synercid resistance among bacteria; 8) the lack of in vitro data relating to what happens to bacteria as they are exposed to increasing concentrations of Synercid over time; 9) the lack of data to assure that the activity of Synercid was indeed neutralized or diluted out in contemporary blood culture bottles; 10) the lack of comprehensive and inclusive data on synergism and antagonism of Synercid with other antimicrobials; and 11) the lack of in vitro data on the serum bactericidal activity of Synercid.

Due to the lack of sufficient data as noted above it is recommended that the following phase IV studies be conducted by the applicant: 1) conduct further clinical trials to determine Synercid's efficacy; 2) further define the PAE of Synercid against a spectrum of target pathogens in animal models; 3) provide data as to the concentration of Synercid in the lung tissue of normal as well as infected patients; 4) collect data on the dissemination of Synercid and Synercid and vancomycin resistant *E. faecium* and *E. faecalis* in the hospital setting where Synercid is being used to treat patients; and 5) collect data on the in vitro serum bactericidal activity of Synercid.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA#: 50-747 **REVIEW #1** **REVIEW DATE: 10/7/97**

INTRODUCTION:

This review is of the microbiology data submitted for the antimicrobial Synercid (RP59500) in relation to its in vitro activity and clinical efficacy against *Enterococcus faecium* including vancomycin-resistant strains.

PRE-CLINICAL EFFICACY (IN VITRO)

SPECTRUM OF ACTIVITY:

Synercid belongs to the streptogramin class of antibiotics. Each member of the class is a combination of at least two structurally unrelated molecules. Synercid is composed of quinupristin, a peptide macrolactone classified as a streptogramin B antibiotic and dalfopristin, a polyunsaturated macrolactone classified as a streptogramin A antibiotic.

Synercid has been shown to have in-vitro activity against the following gram-positive organisms: *Staphylococcus aureus*, including [redacted] and erythromycin- resistant strains, *Staphylococcus epidermidis* including [redacted] resistant strains, *Streptococcus pyogenes, Streptococcus agalactiae, S. pneumoniae, Streptococcus mitis, Streptococcus sanguis, Streptococcus bovis, Streptococcus anginosus, E. faecium including vancomycin-resistant strains, Haemophilus influenzae, Moraxella catarrhalis, Clostridium perfringens, and Bacteriodes* species (1, 2, 3). (Table 1)

Each component of Synercid is metabolized into microbiologically active metabolites. The main metabolites of quinupristin are RP 69012 and RPR 100391 and the major and minor metabolites respectively of dalfopristin are RP 12536 and RP 46790. The metabolites of quinupristin were shown to have MICs two-fold higher than that of the parent compound against the targeted pathogens i.e. *S. aureus*, including inducibly and constitutively erythromycin-resistant (macrolides, lincosamides, streptogramin B(MLS_BI; MLS_BC) strains; *S. epidermidis*, *S. pneumoniae*, including penicillin-resistant and erythromycin-resistant strains; *Streptococcus* spp.; and *E. faecium*, including a vancomycin-resistant strain. Dalfopristin's major metabolite frequently has MICs two-fold lower than that of the parent compound against the target organisms. Dalfopristin's minor metabolite has MICs comparable to two-fold lower than the parent compound against strains of *S. pneumoniae* and *Enterococcus* spp., and two to four-fold higher against strains of *S. aureus*. These various metabolites have been shown not to be antagonistic to either of the parent compounds. Other degradates and impurities of both quinupristin and dalfopristin showed less activity against the targeted pathogens than either parent compound except for a degradate of dalfopristin (RP 75636) which generally has two-fold more active than the parent compound.

The MICs of Synercid against *Enterococcus faecalis* are in the range which are not achievable in-vivo. Thus it cannot be used to treat infections caused by this organism.

Synercid is not active in-vitro against *Enterobacteriaceae* and *Pseudomonas aeruginosa* thus its use in the treatment of infections caused by these organisms is not possible (4).

MECHANISM(S) OF ACTION:

MECHANISM(S) OF RESISTANCE:

Synercid is active against vancomycin-susceptible and resistant *E. faecium*.

Resistance of the enterococci to vancomycin can be either of the intrinsic or acquired type. Acquired resistance phenotypes to vancomycin have been characterized. The *van*A type confers high-level inducible resistance whereas the *van*B type displays variable levels of inducible resistance to vancomycin in both *E. faecalis* and *E. faecium*. Vancomycin resistance of the intrinsic type (*van* C) is most commonly seen in *Enterococcus gallinarium*, *Enterococcus casseliflavus*, and *Enterococcus flavescens*. This *van*C phenotype is thought to be chromosomally encoded and expressed constituitively, although recent data suggest that it may be inducible in certain strains of *E. gallinarium*. The *van*A gene cluster has been identified in strains of *E. gallinarium* and *E. casseliflavus* conferring in these species higher levels of resistance to vancomycin

(MICs of >256μg/mL) than normally anticipated and also resulting in resistance to [redacted] The clinical significance of this finding is unclear at this time but this finding demonstrates the potential for these resistance mechanisms to be shared among the various species of enterococci increasing the possibility for infections with these organisms to be more refractive to treatment.

Resistance to Synercid in *E. faecium* can be due to the sat_A (streptogramin acetyltransferase) and/or the vat_A (virginiamycin acetyltransferase) genes. These plasmid-associated genes code for an enzyme that inactivates streptogramin group A compounds and creates high-level resistance to the combined streptogramins A and B. Three mechanisms of resistance to quinupristin are known: enzymatic modification of the drug, active antibiotic efflux, and modification of the drug target. Generally resistance to A compounds (dalfopristin) is associated with resistance to the mixtures of A and B (quinupristin) compounds, whereas resistance to B compounds is not necessarily associated with resistance to the combination. The mechanism of intrinsic resistance of *E. faecalis* to the streptogramins and lincosamides is unknown (10, 11).

In-vitro studies to assess the potential for the emergence of resistant strains of *E. faecium* to occur during therapy by exposing strains of the organism to doubling dilutions of Synercid have been conducted. One such study (7) noted that *E. faecium* could indeed become resistant to Synercid by such procedures. An interesting finding in this study was that those stains which developed elevated MICs of $\geq$16μg/mL generally did not revert back to be susceptible when they were transferred in broth media not containing the antibiotic. Organisms which developed resistance to <8μg/mL were found to revert back to being susceptible to Synercid. The authors suggest that resistance seen at an MIC$\geq$16μg/mL may be caused by stable mutation(s) not readily reversed.

Antibiotics belonging to the streptogramin family share with macrolides and lincosamides a comparable mode of action inhibiting protein synthesis in bacteria by affecting ribosome function. Cross resistance to macrolides, lincosamides and streptogramin B (MLS_B)-type antibiotics (MLS_B phenotype), resulting from target modification by a methylase, is the most common mechanism of acquired resistance to these antibiotics, present in the majority of enterococci. Expression of MLS_B may be inducible or constitutive. Quinupristin and the combination of quinupristin and dalfopristin has been shown to induce resistance to quinupristin but not to dalfopristin or the combination of these two antibiotics (10, 12).

When streptogramin group A resistance determinants are combined with streptogramin group B resistance determinants the resulting level of resistance to Synercid is $\geq$4μg/mL.

The clinical significance of these various resistance mechanisms as they relate to the combination of quinupristin and dalfopristin (Synercid) is unclear at this time. However, the data to date about these mechanisms of resistance and the ability of some of them to

be transferred within the genus *Enterococcus* and between genera of bacteria strongly suggests that resistance to the quinupristin/dalfopristin combination will most likely occur. Rigorous surveillance for such resistant organisms is critical. Patients treated with the combination drug should be monitored for development of resistant organisms and during therapy kept isolated from other patients so as to prevent the spread of such organisms if they should occur.

EPIDEMIOLOGY:

Due to the fact that Synercid represents a new class of antibiotics there is no data base from which to determine what the incidence of resistance to this antimicrobial is in any treatment population group. Based on the in-vitro data showing cross-resistance between macrolides, lincosamides and streptogramins and the fact that organisms with one mechanism of resistance could already exist in the environment (7) it is postulated that resistance will develop over a moderate amount of time in the clinical setting.

Six incidences of emerging resistance were documented in the emergency use program all involving *E. faecium* going from a MIC of $\leq$1.0μg/mL to $\geq$4.0μg/mL. The clinical trial data in this application have also documented two incidences of *E. faecium* going from the susceptibility category to the intermediate category. In addition, emergence of resistance during therapy has been documented in the literature (13).

The effect of Synercid treatment for 5 days (7.5mg/kg, Q12h) on the fecal microbial flora in humans was determined. On day 3 of treatment fecal concentrations of Synercid were 98$\pm$ 26μg/g. One day after treatment ended the concentration decreased by 33%. During the immediate post-treatment period a temporary decrease in sporulated anaerobes and short-term increases in Synercid-resistant (growth in 10μg/mL) sporulated anaerobes and *Enterobacteriaceae* occurred, all of which returned to normal within 2 weeks. However, 2-4 $\log_{10}$ increases in the total enterococcal as well as the erythromycin-resistant and Synercid-resistant enterococcal subpopulations persisted in the presence of high fecal concentrations of Synercid. The erythromycin and Synercid-resistant enterococci persisted in the absence of Synercid on day 14 or 15 and on day 35 $\pm$ 2. Vancomycin-resistant enterococci were not detected at any time during the 35 day period. There appeared to be, however, a return to baseline for total enterococci by 4 weeks after treatment. The applicant states in the submission that "there may be a risk of translocation of Synercid-resistant enterococci, especially *E. faecalis*, through the intestinal mucosa in certain hospitalized patients, at least in the short-term period following treatment. The possibility of nosocomial transmissions also exists".

Studies to determine the effect of Synercid treatment on VREF$_{\text{ecium}}$ colonization of the GI tract were conducted. In VREF$_{\text{ecium}}$-colonized mice who received Synercid by the oral route for 14 days, only a 7 day eradication of VREF$_{\text{ecium}}$ was observed. In a human study, similar colony counts of VREF$_{\text{ecium}}$ from feces were obtained from VREF$_{\text{ecium}}$-

colonized vs infected patients, the latter group being treated with Synercid, doxycycline or chloramphenicol. The applicant states: "Consequently, such studies suggest the Synercid is not likely to be effective in long-term eradication of VREF$_{aecium}$ from the GI tract and that the risk of transmission from Synercid-treated patients remains a possibility".

POSTANTIBIOTIC EFFECT (PAE):

Postantibiotic effect studies were conducted in order to help determine the optimal dosing regimen for Synercid. The PAE of Synercid in these studies was shown to be dose dependent and varied with the organism being studied.

The in-vitro PAE of Synercid against vancomycin-resistant *E. faecium* and vancomycin-susceptible enterococci ranged from 0.92 to 7.0 hours and 5.5 hours respectively.

INTRACELLULAR CONCENTRATIONS:

ANTIBACTERIAL INTERACTION WITH OTHER ANTIBIOTICS

Studies investigating the potential for synergism or antagonism to occur between Synercid and other antimicrobials have been performed in vitro by either the Synergism between Synercid and novobiocin while demonstrated with some strains of vancomycin-resistant *E. faecium* was not universal. Antagonism between Synercid and gentamicin, doxycycline, and chloramphenicol was not seen with more than a single strain of *E. faecium*.

Synergy of Synercid with doxycycline, amoxicillin, doxycycline/tetracycline and ampicillin was demonstrated against vancomycin-susceptible strains of *E. faecalis*.

Data presented in the application as to the synergism or antagonism of Synercid with other antimicrobials was sketchy at best. Further studies are needed.

PRE-CLINICAL (IN VITRO) - SUSCEPTIBILITY TEST METHODS:

In-vitro susceptibility test methods (MIC and agar disc diffusion) were developed using National Committee for Clinical laboratory Standards (NCCLS) guidelines. The sponsor had several laboratories look at the effects of media composition, pH, inoculum level, length of incubation and temperature of incubation and addition of blood or serum to test media on the outcome of susceptibility test results. These studies did not indicate any reason to deviate from the methods as outlined by the NCCLS for either MIC or agar disc diffusion determination of an isolates susceptibility to Synercid. It should be noted, however, that variations in the MIC results would be observed if gram-positive organisms are tested on blood-supplemented media. Generally the MIC values from blood-supplemented media may be +/- two-fold different than the MIC determined without blood (14).

RATIO OF COMPONENTS FOR SUSCEPTIBILITY TESTING

Studies looking at the total concentration and the ratio of the two components of Synercid that should be incorporated into the susceptibility disc showed that a 15μg total concentration of Synercid with a 70:30 ratio of dalfopristin:quinupristin would accurately determine susceptibility to Synercid. The 70:30 ratio of the two components was also shown to be the ratio which needed to be maintained when dilution susceptibility was done in order to accurately determine susceptibility of organisms by this method (15).

BACTERICIDAL VS BACTERIOSTATIC DETERMINATION

MIC/MBC Ratios: Standard broth dilution assays for determining minimal bactericidal concentrations(MBC) were performed. The MBC was defined as the lowest concentration of Synercid which killed 99.9% of the starting inoculum. The starting inoculum was not stated in the application.

Enterococcus species: The MIC_{90}:MBC_{90} ratio for *E. faecium* ranged from 2 to >100 while the ratio for *E. faecalis* ranged from 2 to >4 in information provided by the applicant.

The demonstration of bactericidal activity of Synercid against *E. faecium* has been shown to be influenced by the erythromycin susceptibility of the isolate, inoculum growth phase and the length of the incubation time of the counting plates (16).

Synercid has been shown in-vitro to be static against strains of *E. faecium* that are of the phenotype MLS_B whether of the inducible or constitutive type. In a rabbit endocarditis model Synercid was shown to be ineffective against two inducibly MLS_B-resistant *E. faecium* strains.

Technical factors which have been shown to influence the determination of the static vs the cidal nature of Synercid are: 1) the use of a log-phase inoculum or a stationary-phase inoculum. A log-phase inoculum has been shown to demonstrate the static nature of Synercid's activity against *E. faecium*; 2) incubation of the counting plates for a period of 48 hours rather than 24 hours has been shown to enhance the detection of the static nature of Synercid against strains of *E. faecium* that are intermediately-susceptible as well as resistant to erythromycin (16).

QUALITY CONTROL PARAMETERS FOR SUSCEPTIBILITY TESTING

Quality control limits for Synercid MIC and agar disc diffusion methods were determined *E. faecalis* in a multi-center study to be as indicated below. These values had been accepted by the Food and Drug Administration and the National Committee for Clinical Laboratory Standards (NCCLS) subcommittee in June 1996 (17, 18). A review of this data did not reveal any reason to suggest control values different then those previously determined.

Organism	Zone QC Limits(mm)	MIC QC Limits(μg/mL)
E. faecalis ATCC 29212	NA	2.0 - 8.0
S. aureus ATCC 25923	23-29	NA

NA = Not applicable

PROVISIONAL INTERPRETIVE CRITERIA FOR SUSCEPTIBILITY TESTING

In order to establish the provisional interpretive criteria for determining whether a bacterial isolate was susceptible or resistant to the 70:30 ratio of dalfopristin to quinupristin quantitative [minimal inhibitory concentration (MIC)] susceptibility testing of a variety of clinical isolates was done by NCCLS methods. This data was correlated with pharmacokinetic and pharmacodynamic information to establish interpretive MIC breakpoints.

In vitro susceptibility test results (MIC_{90}) and MIC range of Synercid against target pathogens are summarized in Table 1.

Table 1. Activity (MIC_{90}) of Synercid against target organisms tested in the United States and other countries.

Organism	Country	No. of strains	MIC(μg/mL) MIC_{90}	MIC(μg/mL) Range
E. faecium	US	1065	1.0	
	UK	178	1.0	
	France	67	1.0	
E. faecium (Van R)	US	1025	1.0	
	UK	110	1.0	
E. faecium (VAN A)	US	791	1.0	
	UK	29	0.5	
E. faecium(VAN B)	US	199	1.0	
	UK	11	2.0	
E. faecium(Van S)	US	40	2.0	
	UK	63	1.0	
	France	44	1.0	

Summary and comments on Table 1 data (comments refer to US isolates unless otherwise noted):

The minimum concentration of Synercid required to inhibit 90% of the *E. faecium* tested was ≤2.0μg/mL. If the vancomycin susceptible *E faecium* and the VAN B types are excluded 90% of the isolates would be inhibited by ≤1.0μg/mL. Published studies have indicated ≤4.0μg/mL to inhibit 90% of *E. faecium* (19).

PRE-CLINICAL (IN VIVO)

PHARMACOKINETICS:

In vitro binding of quinupristin and dalfopristin to serum proteins was determined to be 55 to 78% and 11 to 26% respectively. Elimination of quinupristin and dalfopristin occurs primarily by fecal excretion, with 69% and 66% respectively of the single dose administered eliminated by 96 hours post-dosing. After seven days, 15% and 19% respectively was eliminated through the kidneys.

Penetration of either component of Synercid or RP 12536 into broncho-alveolar lavage fluid was not demonstrated in healthy human volunteers. The applicant attributes this to technical problems related to handling the specimens before they were assayed and possibly the use of non-infected rather than infected human volunteers. The degree of penetration of Synercid into animal lung tissue was demonstrated. It was found that penetration into lung tissue did not increase proportionally to the dose. Determination of serum bactericidal levels was not possible due to technical difficulties attributable to stabilization of the serum and use of 100% serum rather than 50% serum as usually done. The sponsor states that work is being done to optimize this procedure.

PHARMACODYNAMICS:

The 24-hour cumulative dose or area-under-the-concentration vs time curve (AUC) or the amount of drug exposure was shown by two animal models to be the pharmacokinetic parameter that correlates best with the in-vitro activity of Synercid. The AUC_{24} equals ~ 53μg•h/mL with the AUC/MIC equaling 53 for a q8hr dose and ~34 for a q12hr dose.

Synercid was tested against a variety of target pathogens in discriminatory animal models of infection.

In rat and rabbit models of endocarditis induced by MLS_BS and MLS_BI strains of *S. aureus* Synercid when given at a dose of q8h(30mg/kg) IM reduced CFU/mL in vegetations by three to four log_{10}. However, this same dose of Synercid did not reduce the CFU/mL of MLS_BC strains of MRSA to the same extent even though in-vitro the organism was found to be susceptible. The explanation for this apparent discrepancy between the in-vitro and in-vivo findings was that each Synercid component displayed a different diffusion pattern as noted by autoradiography studies into the cardiac vegetation. Quinupristin, displayed a homogeneous diffusion whereas dalfopristin showed a decreased gradient of concentration between the periphery and the core of the vegetation (12, 21). This model was used to demonstrate the necessity of maintaining a consistent level of dalfopristin in such lesions in order to achieve bactericidal activity against bacteria.

In a rabbit model of vancomycin-resistant *E. faecium* induced endocarditis MLS_BI strains were associated with a decreased efficacy of Synercid.

TENTATIVE SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

MIC Breakpoints: Based on the pharmacokinetic profile of Synercid and in vitro susceptibility testing of target pathogens provisional breakpoints of $\leq 1\mu g/mL$ indicating susceptibility, $2\mu g/mL$ for intermediate susceptibility, and $\geq 4\mu g/mL$ for resistant to Synercid were chosen for the clinical trials.

Disc provisional interpretive criteria: Based on the "error-rate bounded method" using the provisional MIC noted above, two provisional disc interpretive criteria were determined for the $15\mu g$ Synercid disc:

Proposed zone diameter criteria (mm)			% Interpretive Error		
Susceptible	Intermediate	Resistant	Very Major	Major	Minor
$\geq 19^a$	16-18	≤ 15	0.0	0.0	1.9
$\geq 18^b$	ND	≤ 17	1.9	0.0	NA

[a] Based on: $\leq 1\mu g/mL$ = susceptible; $2\mu g/mL$ = intermediate; $\geq 4\mu g/mL$ = resistant
[b] Based on: $\leq 2\mu g/mL$ = susceptible; $\geq 4\mu g/mL$ = resistant
ND = Not determined
NA = Not applicable

CLINICAL EFFICACY:

CLINICAL MICROBIOLOGY:

Isolates - Relevance to Proposed Indications:

Infections due to vancomycin-resistant *Enterococcus faecium*, including cases associated with concurrent bacteremia.

The above organisms are clinically associated with the stated indications and in-vitro susceptibility test data indicates that Synercid has activity against this organism thus the indications\organism combination is appropriate for this antimicrobial.

CLINICAL TRIAL DATA

Overall Correlation of Therapeutic Data with Reference Laboratory MICs

Analysis by the sponsor of the treatment outcome data for "systemic infection with vancomycin-resistant *E. faecium*" using the provisional susceptibility breakpoints of: ≤1μg/mL = susceptible; 2μg/mL = intermediate; ≥4μg/mL = resistant revealed the following.

Infections Due to Vancomycin-Resistant *E. faecium* Including Cases Associated with Concurrent Bacteremia (Emergency Use Case Program)

Clinical studies under the "Emergency Use Case Program" were open-labeled prospective trials. Patients enrolled in this program received Synercid at a dose of 7.5mg/kg IV Q8h for up to 14 days. Data was analyzed by the company and reviewed for completeness and accuracy.

The majority of the pathogens treated under the protocols (JRV398, JRV398B and JRV301) covering this category were vancomycin-resistant *E. faecium* (88%). Ninety-one percent (167/184) of the vancomycin-resistant *E. faecium* isolates had MICs of ≤1μg/mL. Approximately 72% (121/167) of the cases with these isolates had satisfactory pathogen responses and clinical responses. Only six (6) of 10 (60%) strains and 1 of 2 (50%) strains with MICs of 2 and 4μg/mL respectfully correlated with satisfactory pathogen and clinical responses.

Overall Correlation of Therapeutic Data with Reference Zone Diameters

Analysis by the sponsor of the treatment outcome data for "systemic infection with VREF*aecium*" using the provisional susceptibility disk diffusion interpretive criteria of ≥19mm = susceptible, 16-18mm = intermediate, and ≤15 = resistant revealed the following.

Emergency Use Care Program

Satisfactory pathogen response

Approximately 69% of patients infected with VREF$_{aecium}$ which had zone diameters of ≥19mm had satisfactory pathogen responses.

Two out of three patients with VFEF$_{aecium}$ isolates which had zone diameters of 16-18mm and one patient with a VREF$_{aecium}$ isolate with a zone diameter of ≤15mm had satisfactory pathogen responses.

Satisfactory clinical response

Approximately 71% of patients infected with VREF$_{aecium}$ that had zone diameters of

≥19mm had satisfactory clinical responses.

Two out of three patients with VREF$_{faecium}$ isolates which had zone diameters of 16-18mm and one patient with a VREF$_{faecium}$ isolate with a zone diameter of ≤15mm had satisfactory clinical responses.

Use of the alternate disk diffusion criteria, ≥20mm = S; ≤16mm = R for both of the above gave similar correlation's in each respective case.

FINAL MIC BREAKPOINTS:

Based on MIC correlation of clinical isolates with therapeutic outcome and pathogen eradication the provisional MIC breakpoints of ≤1μg/mL = susceptible, 2μg/mL = moderately susceptible, and ≥4μg/mL = resistant for *E. faecium* seem appropriate MIC breakpoints.

FINAL DISC INTERPRETIVE CRITERIA:

Analysis of the correlation of the final MIC breakpoints with zone diameters determined with the same clinical isolates used to determine the MIC breakpoint reveals the following:

Proposed zone diameter criteria (mm)			% Interpretive Error		
Susceptible	Intermediate	Resistant	Very Major	Major	Minor
≥19	16-18	≤15	1(0.1)	2(0.2)	73(5.8)
≥19	17-18	≤16	1(0.1)	6(0.4)	70(5.6)
≥20	**17-19**	**≤16**	**1(0.1)**	**6(0.4)**	**104(8.3)**
≥21	17-20	≤16	1(0.1)	6 (0.4)	171(13.7)
≥21	18-20	≤17	1(0.1)	14(1.1)	161(12.9)
≥22	18-21	≤17	0	14(1.1)	220(17.6)

Based on this analysis the choice of ≥20mm (S), ≤16mm(R) seems appropriate for the interpretive zone diameter criteria. While more conservative than the original provisional zone diameter criteria of ≥19 (S), ≤15mm (R) the percentage of intermediate zone diameters is increased only by 2.5% and seems more appropriate for a new molecular entity for which there is uncertainty as to whether the majority of resistant isolates will be detected by using a 15μg Synercid disk.

Using the indicated zone size diameters versus the ≥19 = S, ≤15= R does not change the very major or major errors for *E. faecium* . The minor error for *E. faecium* changes from 5.4% for the ≤15mm to 5.8% for the ≤16mm criteria.

CONCLUSIONS AND RECOMMENDATIONS:

The in-vitro data to support the provisional MIC breakpoints and disk diffusion zone size interpretation as well as the quality control and potential effects that variations in the pH, inoculum concentration etc. might have on susceptibility test results were adequately studied. The provisional MIC breakpoints (≤1μg/mL = susceptible, ≥4μg/mL = resistant) seemed adequate to predict clinical outcome. The provisional disk diffusion criteria (≤15mm = resistant, ≥19mm = susceptible) also appeared to be adequate to determine clinical outcome. However, it is felt that a more conservative disk diffusion interpretive criteria (≤16mm = resistant, ≥20mm = susceptible) would be more appropriate because of the bacteriostatic nature of this antimicrobial and because of the question as to whether or not using the combination of dalfopristin/quinupristin vs dalfopristin alone will detect the majority of resistant strains of critical pathogens such as vancomycin-resistant *E. faecium.*

In-vivo animal data to study the pharmacokinetics and pharmacodynamics of the drug provided information that indeed the dalfopristin/quinupristin (Synercid) combination is not bactericidal against *E. faecium* and may not be bactericidal against certain strains of other organisms such as methicillin-resistant *S. aureus* with constitutive resistance to erythromycin (MLS_BC). Further work by the applicant in this area is needed to define whether the dosing is adequate and whether the 70/30 ratio of dalfopristin to quinupristin is appropriate.

Under **INDICATIONS AND USAGE** in the package insert a note indicating that the antimicrobial is not active against *E. faecalis* has been added.

Information as to the potential spread of Synercid resistant *E. faecium* as well as the potential spread of *E. faecalis* between hospitalized patients treated with Synercid was not presented in spite of the fact that the applicant noted in the submission that in deed their was this possibility. It has been suggested that in the package insert under precautions that a statement be made of this potential.

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SYNERCID PACKAGE INSERT DRAFT

Microbiology: The streptogramin components of Synercid, quinupristin, and dalfopristin [redacted] in a ratio of 30 parts quinupristin to 70 parts dalfopristin. These two components act synergistically so that Synercid's [redacted] metabolites also contribute to the antimicrobial activity of Synercid. [redacted] in vitro synergism of the major metabolites with the complementary parent compound has been demonstrated.

[redacted]

Aerobic gram-positive microorganisms

Enterococcus faecium **(vancomycin-resistant strains only)**

NOTE: [redacted]

SUSCEPTIBILITY TESTS:

[redacted]

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of [redacted]. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution[1] method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of [redacted]. The MIC values should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤1	Susceptible(S)
2	Intermediate
≥4	Resistant(R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the [redacted] alternative, clinically feasible drugs, the test should be repeated. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

A standardized susceptibility test procedure requires the use of laboratory control organisms to control technical aspects of the laboratory procedures. Standard dalfopristin/quinupristin [redacted] should provide the following MIC value with this quality control strain:

Microorganism	MIC (µg/mL)
E. faecalis [redacted] 29212	2 to 8

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15µg [redacted] (Synercid) to test the susceptibility of microorganisms to [redacted]

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15µg dalfopristin/quinupristin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for dalfopristin/quinupristin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique the 15µg dalfopristin/quinupristin disk should provide the following zone diameters with this laboratory test quality control strain:

Microorganism	Zone Diameter (mm)
S. aureus [redacted]25923	23-29

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The following needs to be included under **PRECAUTIONS**

/S/ 3/4/98

Frederic J. Marsik, Ph.D.
Review Microbiologist

HFD-530 Div. File

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

AUG 27 1998

NDA#: 50-748 **REVIEW #1** **REVIEW DATE: 7/30/98**

SUBMISSION TYPE:	DOCUMENT DATE:	CDER DATE:	ASSIGNED DATE:
NDA	9/5/97	9/8/97	9/9/97

NAME AND ADDRESS OF APPLICANT:

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DRUG PRODUCT NAME:

Proprietary:	Synercid
Nonproprietary:	Quinupristin/Dalfopristin
Code Names/#'s:	RP59500(RP57669/RP54476)
Chemical Formula(empirical):	Quinupristin = $C_{53}H_{67}N_9O_{10}S$
	Dalfopristin = $C_{34}H_{50}N_4O_9$

INDICATIONS:

Complicated skin and skin structure infections

[redacted]

Infections due to vancomycin-resistant *Enterococcus faecium* including cases with concurrent bacteremia

Infections caused by *Staphylococcus aureus* including [redacted] susceptible and resistant isolates

DOSAGE FORM: [redacted]
STRENGTH:
ROUTE OF ADMINISTRATION: Intravenous

RELATED DOCUMENTS: [redacted]

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

CLINICAL MICROBIOLOGY REVIEW

NDA#: 50-748 **REVIEW #1** **REVIEW DATE: 7/30/98**

REMARKS/COMMENTS:

The microbiology portion of this application is approvabl[redacted]which are non-approvable from the Microbiology perspective due to the lack of data in the submission on the pharmacokinetics of Synercid in the lung. In addition, the application is approvable on the condition that the indicated changes be incorporated into the labeling.

It is noted that this submission lacks details in the following areas which may have helped clarify data provided and which may have helped to assess the true efficacy and safety of the drug when used in the clinical setting. These areas are:

1) The small numbers of patients within each of the proposed indications with methicillin-resistant *Staphylococcus aureus* (MRSA) and MLS_BC strains of *S. aureus*, and *Enterococcus faecium* which were available to evaluate in order to ascertain Synercid's efficacy. Larger numbers of patients would have made for more reliable assessment of bacteriological eradication and clinical efficacy.
2) The lack of data on the activity of each of the components of Synercid against bacterial isolates. This type of data would have allowed for an analysis of whether susceptibility testing with an individual component may have been a better way to predict the efficacy of Synercid and allowed for separating the constitutively resistant strains of *S. aureus* from the inducible and susceptible strains.
3) The lack of epidemiologic data relating to the dissemination of vancomycin-resistant *E. faecium* (VRE*faecium*), vancomycin-resistant *E. faecalis* (VRE*faecalis*), Synercid and Synercid and vancomycin resistant *Enterococcus faecium* and *faecalis* in the hospital setting in which Synercid was used despite the fact that the applicant in their submission noted that the potential for the transmission of resistant organisms was a possibility. This type of information would have provided information about the transmissibility of Synercid resistant organisms between patients.
4) The lack of animal model and human data on the postantibiotic effect against targeted pathogens. This information may have helped explain the lack of efficacy for certain indications.
5) The lack of information discussing the relationship of achievable peak drug concentration to MIC and the emergence of resistance. Such information might have provided an indication on how quickly organisms resistant to Synercid might develop.
6) The lack of data on the transmissibility of Synercid resistance among bacteria. Information of this nature may have provided an indication as to whether resistance to Synercid could be transmitted between bacteria of different genera and species.
7) The lack of in vitro data which assess the emergence of resistance with increasing concentrations of Synercid and time. More comprehensive information may have defined whether or not certain bacteria might develop resistance more rapidly than other bacteria.

8) The lack of data to assure that the activity of Synercid was indeed neutralized or diluted out [redacted] This information might have made the assumption that the organism was eradicated in those patients who had negative blood cultures but expired before finishing therapy more tenable.
9) The lack of comprehensive and inclusive data on synergism and antagonism of Synercid with other antimicrobials. Lack of comprehensive data in this case made it harder to understand any contribution a second antibiotic could be making to treatment successes.
10) The lack of in vitro data on the serum bactericidal activity of Synercid. Information of this nature might have shown what the actual activity of Synercid was in the serum of patients against the infecting pathogen perhaps indicating to a better degree what concentrations of Synercid were required to achieve killing of the pathogen.

Due to the lack of sufficient data as noted above it is recommended that the following phase IV studies be conducted by the applicant:
1) conduct further clinical trials to ascertain Synercid's efficacy;
2) ascertain by in vitro quantitative and qualitative susceptibility testing the susceptibility of constitutively resistant strains of *S. aureus* to the components of Synercid and correlate this data with efficacy in animal models and humans treated with Synercid;
3) analyze the data in item 1 to determine if the results from the individual component testing of Synercid can separate out the MLS_BC and MLS_BI strains of bacteria from those without these phenotypes;
4) further define the postantibiotic effect (PAE) of Synercid against a spectrum of target pathogens in animal models;
5) provide data as to the concentration of Synercid in the lung tissue of normal as well as infected patients;
6) provide clinical efficacy data from well controlled studies in a large patient populations with MRSA infections and infections with MLS_BC strains of bacteria;
7) collect data on the dissemination of Synercid and Synercid and vancomycin-resistant *E. faecium* and *E. faecalis* in the hospital setting where Synercid is being used to treat patients, and
8) collect data on the in vitro serum bactericidal activity of Synercid.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
NDA#: 50-748 REVIEW #1 REVIEW DATE: 7/30/98

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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
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INTRODUCTION:

This review is of the microbiology data submitted for the antimicrobial Synercid (RP59500) in relation to its in vitro activity and clinical efficacy against various species of staphylococci, including [redacted] resistant *Staphylococcus aureus, Streptococcus pneumoniae (penicillin susceptible and resistant isolates)* and *Enterococcus faecium* including vancomycin-resistant strains and other gram-positive organisms associated with specific infections.

PRE-CLINICAL EFFICACY (IN-VITRO)

SPECTRUM OF ACTIVITY

Synercid belongs to the streptogramin class of antibiotics. Each member of the class is a combination of at least two structurally unrelated molecules. Synercid is composed of quinupristin, a peptide macrolactone classified as a streptogramin B antibiotic and dalfopristin, a polyunsaturated macrolactone classified as a streptogramin A antibiotic.

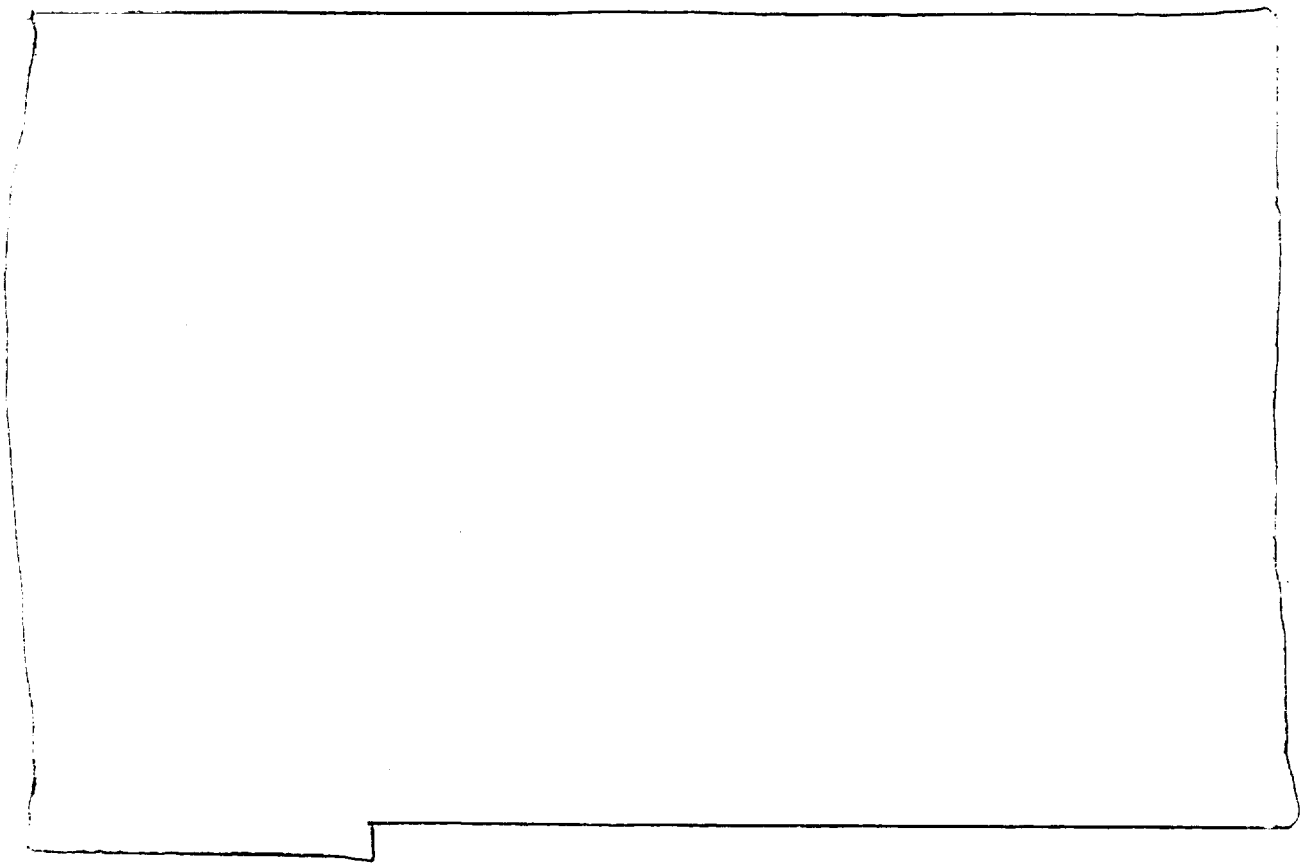
Synercid has been shown to have in-vitro activity against the following gram-positive organisms: *Staphylococcus aureus*, including methicillin and erythromycin- resistant strains, *Staphylococcus epidermidis* including methicillin-resistant strains, *Streptococcus pyogenes, Streptococcus agalactiae, S. pneumoniae, Streptococcus mitis, Streptococcus sanguis, Streptococcus bovis, Streptococcus anginosus, E. faecium including vancomycin-resistant strains, Haemophilus influenzae, Moraxella catarrhalis, Clostridium perfringens, and Bacteroides* species(1, 2, 3). See page **13 through 17** for NDA 50-748 data.

Each component of Synercid is metabolized into microbiologically active metabolites. The main metabolites of quinupristin are RP 69012 and RPR 100391 and the major and minor metabolites respectively of dalfopristin are RP 12536 and RP 46790. The metabolites of quinupristin were shown to have MICs two-fold higher than that of the parent compound against the targeted pathogens i.e. *S. aureus*, including inducibly (MLS_BI) and constitutively (MLS_BC) erythromycin-resistant (Macrolides, Lincosamides, Streptogramin B) strains; *S. epidermidis*, *S. pneumoniae*, including penicillin-resistant and erythromycin-resistant strains; *Streptococcus* spp.; and *E. faecium*, including a vancomycin-resistant strain. Dalfopristin's major metabolite frequently has MICs two-fold lower than that of the parent compound against the target organisms. Dalfopristin's minor metabolite has MICs comparable to two-fold lower than the parent compound against strains of *S. pneumoniae* and *Enterococcus* spp., and two to four-fold higher against strains of *S. aureus*. These various metabolites have been shown not to be antagonistic to either of the parent compounds. Other degradates and impurities of both quinupristin and dalfopristin showed less activity against the targeted pathogens than

either parent compound except for a degradate of dalfopristin (RP 75636) which generally has two-fold more active than the parent compound.

The MICs of Synercid against *Enterococcus faecalis* are in the range which are not achievable in-vivo thus it cannot be used to treat infections caused by this organism. Synercid is not active in-vitro against *Enterobacteriaceae* and *Pseudomonas aeruginosa* thus its use in the treatment of infections caused by these organisms is not feasible (4).

MECHANISM(S) OF ACTION



MECHANISM(S) OF RESISTANCE

Vancomycin-resistant enterococci:

Resistance of the enterococci to vancomycin can be either of the intrinsic or acquired type. Acquired resistance phenotypes to vancomycin have been characterized. The *van*A type confers high-level inducible resistance whereas the *van*B type displays variable levels of inducible resistance to vancomycin in both *E. faecalis* and *E. faecium*. Vancomycin resistance of the intrinsic type (*van* C) is most commonly seen in *Enterococcus gallinarium*, *Enterococcus casseliflavus*, and *Enterococcus flavescens*.

This *van*C phenotype is thought to be chromosomally encoded and expressed constituitively, although recent data suggest that it may be inducible in certain strains of *E. gallinarium*. The *van*A gene cluster has been identified in strains of *E. gallinarium* and *E. casseliflavus* conferring in these species higher levels of resistance to vancomycin (MICs of >256μg/mL) than normally anticipated and also resulting in resistance to [redacted]. The clinical significance of this finding is unclear at this time but this finding demonstrates the potential for these resistance mechanisms to be shared among the various species of enterococci increasing the possibility for infections with these organisms to be more refractive to treatment.

Resistance to Synercid in *E. faecium* can be due to the sat_A (streptogramin acetyltransferase) and/or the vat_A (virginiamycin acetyltransferase) genes. These plasmid-associated genes code for an enzyme that inactivates streptogramin group A compounds and creates high-level resistance to the combined streptogramins A and B. Generally resistance to A compounds (dalfopristin) is associated with resistance to the mixtures of A and B (quinupristin) compounds, whereas resistance to B (quinupristin) compounds is not necessarily associated with resistance to the combination. The mechanism of intrinsic resistance of *E. faecalis* to the streptogramins and lincosamides is unknown (10, 11).

In-vitro studies to assess the potential for the emergence of resistant strains of *E. faecium* to occur during therapy by exposing strains of the organism to doubling dilutions of Synercid have been conducted. One such study (7) noted that *E. faecium* could indeed become resistant to Synercid by such procedures. An interesting finding in this study was that those stains which developed elevated MICs of ≥16μg/mL generally did not revert back to be susceptible when they were transferred in broth media not containing the antibiotic. Organisms which developed resistance to <8μg/mL were found to revert back to being susceptible to Synercid. The authors suggest that resistance seen at an MIC≥16μg/mL may be caused by stable mutation(s) not readily reversed.

Antibiotics belonging to the streptogramin family share with macrolides and lincosamides a comparable mode of action inhibiting protein synthesis in bacteria by affecting ribosome function. Cross resistance to macrolides, lincosamides and streptogramin B (MLS_B)-type antibiotics (MLS_B phenotype), resulting from target modification by a methylase, is the most common mechanism of acquired resistance to these antibiotics, present in the majority of enterococci. Expression of MLS_B may be inducible or constitutive. Quinupristin and the combination of quinupristin and dalfopristin has been shown to induce resistance to quinupristin but not to dalfopristin or the combination of these two antibiotics (10, 12).

The major mechanism of Synercid resistance in staphylococci has been reported to be resistance to dalfopristin mediated by the *vat*, and *vga* genes. The *vat* genes code for enzymes which degrade streptogramin A compounds (ex: dalfopristin). The *vga* gene codes for a protein mediating efflux of streptogramin group A compounds outside of

cells. These genes are reported to be plasmid mediated but only the vat_B gene to date has been shown to be transferable by conjugation (13, 14). Streptogramin and erythromycin are inducers of this resistance mechanism(15).

Resistance or decreasing susceptibility of staphylococci to streptogramin B (e.g. quinupristin) has been associated with *vgb* (virginiamycin B) or *erm*(erythromycin ribosome methylation) genes. The *vgb* gene mediates enzymatic hydrolysis of streptogramin B compounds. The *vgb* gene to date has only been found on plasmids associated with staphylococci. The *erm* gene series has been found to code for an enzyme which modifies the ribosomal target resulting in cross-resistance to macrolides, lincosamides, and streptogramin group B compounds. The erm genes have been reported to be chromosomal or plasmid-mediated. The *msr*A (macrolide streptogramin resistance) gene confers resistance to 14- and 15- carbon ring macrolides including erythromycin (15). Streptogramin B components are not inducers, but induction with erythromycin results in cross resistance to the streptogramin component. This has been referred to as the MS phenotype (15).

When streptogramin group A resistance determinants are combined with streptogramin group B resistance determinants the resulting level of resistance to Synercid is $\geq$4µg/mL.

Resistance mechanism in *Streptococcus pneumoniae* have not been fully elucidated. In the pneumococci, as in the enterococci, quinupristin is an efficient inducer of the inducible cross-resistant MLS_B phenotype. Nevertheless Synercid demonstrates good in-vitro and in-vivo activity against MLS_B inducible pneumococci. It is postulated that this good activity against pneumococci in contrast to the enterococci is due to the rapid bactericidal activity of Synercid against pneumococci thus induction has no time to occur (7).

The clinical significance of these various resistance mechanisms as they relate to the combination of quinupristin and dalfopristin (Synercid) is unclear at this time. However, the data to date about these mechanisms of resistance and the ability of some to be transferred within the genus *Enterococcus* and between genera strongly suggests that resistance to the quinupristin/dalfopristin combination will most likely occur. Rigorous surveillance for such resistant organisms is critical. Patients treated with the combination drug should be monitored for development of resistant organisms and during therapy kept isolated from other patients so as to prevent the spread of such organisms if they should occur.

EPIDEMIOLOGY

Due to the fact that Synercid represents a new class of antibiotics there is no data base from which to determine what the incidence of resistance to this antimicrobial is in any treatment population group. Based on the in-vitro data showing cross-resistance between

macrolides, lincosamides and streptogramins it is postulated that resistance will develop within 3 to five years of its general introduction. In addition, based on the facts that there are already organisms resistant to the quinupristin in the environment and that stable resistance to Synercid in *E. faecium* can come about when exposed in a step wise fashion to increasing concentrations of the antimicrobial, the likelihood of resistance occurring to Synercid is great.

This premise is supported by data provided in this submission for a patient enrolled in a [redacted] study. The MIC's of *S. aureus* went from 0.5μg/mL to 8.0μg/mL. Six incidences of emerging resistance were documented in the emergency use program all involving *E. faecium* going from a MIC of ≤1.0μg/mL to ≥4.0μg/mL. The clinical trial data in this application have also documented two incidences of *E. faecium* going from the susceptibility category to the intermediate category. In addition, emergence of resistance during therapy has been documented in the literature (16).

The effect of Synercid treatment for 5 days (7.5mg/kg, Q12h) on the fecal microbial flora in humans was determined. On day 3 of treatment fecal concentrations of Synercid were 98± 26μg/g. One day after treatment ended the concentration decreased by 33%. During the immediate post-treatment period a temporary decrease in sporulated anaerobes and short-term increases in Synercid-resistant (growth in 10μg/mL) sporulated anaerobes and *Enterobacteriaceae* occurred, all of which returned to normal within 2 weeks. However, 2-4 $\log_{10}$ increases in the total enterococcal as well as the erythromycin-resistant and Synercid-resistant enterococcal subpopulations persisted in the presence of high fecal concentrations of Synercid. The erythromycin and Synercid-resistant enterococci persisted in the absence of Synercid on day 14 or 15 and on day 35 ± 2. Vancomycin-resistant enterococci were not detected at any time during the 35 day period. There appeared to be, however, a return to baseline for total enterococci by 4 weeks after treatment. The applicant states in the submission that "there may be a risk of translocation of Synercid-resistant enterococci, especially *E. faecalis*, through the intestinal mucosa in certain hospitalized patients, at least in the short-term period following treatment. The possibility of nosocomial transmissions also exists".

Studies to determine the effect of Synercid treatment on $VREF_{aecium}$ colonization of the GI tract were conducted. In $VREF_{aecium}$-colonized mice who received Synercid by the oral route for 14 days, only a 7 day eradication of $VREF_{aecium}$ was observed. In a human study, similar colony counts of $VREF_{aecium}$ from feces were obtained from $VREF_{aecium}$-colonized vs infected patients, the latter group being treated with Synercid, doxycycline or chloramphenicol. The applicant states: "Consequently, such studies suggest the Synercid is not likely to be effective in long-term eradication of $VREF_{aecium}$ from the GI tract and that the risk of transmission from Synercid-treated patients remains a possibility".

POSTANTIBIOTIC EFFECT (PAE)

Postantibiotic effect studies were conducted in order to help determine the optimal dosing regimen for Synercid. The PAE of Synercid in these studies was shown to be dose dependent and varied with the organism being studied.

The in vitro PAE of Synercid with *S. aureus* ranged from 1.4 to 7.7 hours when determined using colony counts. In vitro PAEs of Synercid with *S. pneumoniae* and *S. pyogenes* ranged from 7.5 to 9.5 hours and 18 hours respectively. The in-vitro PAE of Synercid with vancomycin-resistant *E. faecium* and vancomycin-susceptible enterococci ranged from 0.92 to 7.0 hours and 5.5 hours respectively.

INTRACELLULAR CONCENTRATIONS

ANTIBACTERIAL INTERACTION WITH OTHER ANTIBIOTICS

Studies investigating the potential for synergism or antagonism to occur between Synercid and other antimicrobials have been performed in vitro by either the Synergism between Synercid and novobiocin while demonstrated with some strains of vancomycin-resistant *E. faecium* was not universal. Antagonism between Synercid and gentamicin, doxycycline, and chloramphenicol was seen with a single strain of *E. faecium*.

Synergy of Synercid with doxycycline, amoxicillin, doxycycline/tetracycline and ampicillin was demonstrated against vancomycin-susceptible strains of *E. faecalis*.

Combination studies conducted using with erythromycin-resistant resistant *S. aureus* demonstrated synergism between Synercid and several cephalosporins. Time-kill studies with a strain of *S. aureus* (MLS_BC) MRSA showed synergism with cefamandole, imipenem and high concentrations of doxycycline. Antagonism was generally not observed.

Data presented in the application as to the synergism or antagonism of Synercid with other antimicrobials was sketchy at best. Further studies are needed.

IN-VITRO - PRE-CLINICAL - SUSCEPTIBILITY TEST METHODS

In-vitro susceptibility test methods (MIC and agar disc diffusion) were developed using National Committee for Clinical laboratory Standards (NCCLS) guidelines. The sponsor had several laboratories look at the effects of media composition, pH, inoculum level, length of incubation and temperature of incubation and addition of blood or serum to test media on the outcome of susceptibility test results. These studies did not indicate any reason to deviate from the methods as outlined by the NCCLS for either MIC or agar disc diffusion determination of an isolates susceptibility to Synercid. It should be noted, however, that variations in the MIC results would be observed if gram-positive organisms are tested on blood-supplemented media. Generally the MIC values from blood-supplemented media may be $\pm$ two-fold different than the MIC determined without blood (17).

RATIO OF COMPONENTS FOR SUSCEPTIBILITY TESTING

Studies looking at the total concentration and the ratio of the two components of Synercid that should be incorporated into the susceptibility disc showed that a 15μg total concentration of Synercid with a 70:30 ratio of dalfopristin:quinupristin would accurately determine susceptibility to Synercid. The 70:30 ratio of the two components was also shown to be the ratio which needed to be maintained when dilution susceptibility was done in order to accurately determine susceptibility of organisms by this method (18).

BACTERICIDAL VS BACTERIOSTATIC DETERMINATION

MBC/MIC Ratios: Standard broth dilution assays for determining minimal bactericidal concentrations(MBC) were performed. The MBC was defined as the lowest concentration of Synercid which killed 99.9% of the starting inoculum. The starting inoculum was not stated in the application.

Enterococcus species: The MBC_{90}:MIC_{90} ratio for *E. faecium* ranged from 2 to >100 while the ratio for *E. faecalis* ranged from 2 to >4 in information provided by the applicant.

Staphylococcus aureus: The MBC_{90}:MIC_{90} ratio for *S. aureus* as a general class ranged from 1 to 3. The resistance phenotype influenced the ratio with generally low MBCs for MLS_BS, and MLS_BI strains and high MBCs for some MLS_BC strains.

Staphylococcus species: MBC_{90}s of Synercid for [redacted] susceptible *S. epidermidis* and [redacted] resistant *S. epidermidis* not characterized for MLS_B phenotype were equal to or 2 times the MIC_{90}s. MBC_{90}s of Synercid against erythromycin-resistant coagulase-negative staphylococci ranged up to 16-fold higher than MIC_{90}s.

Streptococcus species: The MBC_{90}:MIC_{90} for *S. pneumoniae* regardless of susceptibility to penicillin or erythromycin ranged from 1 to >2. For *S. pyogenes*, *S. agalactiae*, *S. bovis* and viridans group streptococci the ratio was equal to or 2-fold greater than the MIC.

The demonstration of bactericidal activity of Synercid against *E. faecium* has been shown to be influenced by the erythromycin susceptibility of the isolate (19). Synercid has been shown, in-vitro, to be static against strains of *E. faecium* that are of the phenotype MLS_B whether of the inducible or constitutive type. In a rabbit endocarditis model Synercid was shown to be ineffective against two inducibly MLS_B-resistant *E. faecium* strains. Constitutive expression of resistance to MLS_B antibiotics also appears to significantly affect the bactericidal activity of Synercid against staphylococci. In both rabbit and rat endocarditis models infections due to constitutively MLS_B-resistant *S. aureus* isolates were not effectively treated. Against pneumococci, the bactericidal activity of this combination appears to be independent of susceptibility or resistance to erythromycin (20).

Technical factors which have been shown to influence the determination of the static vs the cidal nature of Synercid are: 1) the use of a log-phase inoculum or a stationary-phase inoculum. A log-phase inoculum has been shown to demonstrate the static nature of Synercid's activity against *E. faecium*; 2) incubation of the counting plates for a period of 48 hours rather than 24 hours has been shown to enhance the detection of the static nature of Synercid against strains of *E. faecium* that are intermediately-susceptible as well as resistant to erythromycin (19).

QUALITY CONTROL PARAMETERS FOR SUSCEPTIBILITY TESTING

Quality control limits for Synercid MIC and agar disc diffusion methods were determined in a multi - center study to be as indicated below. These values had been accepted by the Food and Drug Administration and the National Committee for Clinical Laboratory Standards (NCCLS) subcommittee in June 1996 (21, 22). A review of this data did not reveal any reason to suggest control values different then those previously determined.

Organism		Zone QC Limits(mm)	MIC QC Limits(μg/mL)
S. aureus	ATCC 25923	23 - 29	NA

S. aureus	ATCC 29213	NA	0.25 - 1.0
S. pneumoniae	ATCC 49619	19 -24	0.25 - 1.0
E. faecalis	ATCC 29212	NA	2.0 - 8.0

NA = Not applicable

PROVISIONAL INTERPRETIVE CRITERIA FOR SUSCEPTIBILITY TESTING

In order to determine the provisional interpretive criteria for determining whether a bacterial isolate was susceptible or resistant to the 70:30 ratio of dalfopristin to quinupristin quantitative [minimal inhibitory concentration (MIC)] susceptibility testing of a variety of clinical isolates was done by NCCLS methods. This data was correlated with pharmacokinetic and pharmacodynamic information to establish interpretive MIC breakpoints.

In vitro susceptibility test results (MIC_{90}) and MIC range of Synercid against target pathogens are summarized in Table 1.

Table 1. Activity (MIC_{90}) of Synercid against target organisms tested in the United States and other countries

Organism	Country	Number of Isolates	MIC_{90} ug/mL	Range ug/mL
Enterococcus faecium	United States (US)	1065	1.00	
	United Kingdom (UK)	178	1.00	
	France	67	1.00	
E. faecium Vancomycin Resistant	US	1025	1.00	
	UK	110	1.00	
E. faecium VAN A genotype	US	791	1.00	
	UK	29	0.50	
E. faecium VAN B genotype	US	199	1.00	
	UK	11	2.00	
E. faecium Vancomycin Susceptible	US	40	2.00	
	UK	63	1.00	
	France	44	1.00	
Enterococcus avium	US	43	4.00	

E. avium Vancomycin Susceptible	US	16	2.00
Enterococcus casseliflavus	US	30	4.00
Enterococcus durans	US	37	4.00
E. durans Vancomycin Susceptible	US	17	4.00
Enterococcus gallinarium	US	32	8.00
Streptococcus agalactiae	US	82	0.50
	UK	34	0.50
	France	85	1.00
Streptococcus bovis	US	33	2.00
Streptococcus milleri	France	13	4.00
Streptococcus mitis	France	14	2.00
Streptococcus pneumoniae	US	1456	0.50
	UK	69	0.50
	France	200	1.00
S. pneumoniae Erythromycin Susceptible	US	1250	0.50
	UK	44	0.50
	France	139	1.00
S. pneumoniae Erythromycin Resistant	US	192	1.00
	UK	25	1.00
	France	67	1.00
S. pneumoniae Penicillin Susceptible	US	940	0.50
	UK	24	0.50
	France	14	0.25
S. pneumoniae Penicillin Intermediate	US	155	1.00
	UK	26	
S. pneumoniae	US	276	1.00
Streptococcus pyogenes	US	783	0.25
	UK	20	0.25

	France	80	1.00
Streptococcus sanguis	US	13	2.00
	France	16	4.00
Viridans group streptococci	US	125	1.00
Haemophilus influenzae	US	809	8.00
	UK	20	8.00
	France	111	8.00
H. influenzae Beta-lactamase +	US	224	8.00
	France	25	8.00
H. influenzae Beta-lactamase -	US	485	8.00
	France		8.00
Moraxella catarrhalis	US	595	0.50
	UK	20	1.00
	France	28	1.00
Neisseria meningitidis	US	105	0.50
Neisseria gonorrhoeae	US	205	0.50
N. gonorrhoeae Beta-lactamase +	US	170	0.50
N. gonorrhoeae Beta-lactamase -	US	31	0.12
Pediococcus spp.	US	22	4.00
Leuconostoc spp.	US	21	2.00
Corynebacterium jeikum	US	30	0.25
Listeria monocytogenes	US	30	1.00
Legionella pneumphila	US	105	1
Legionella spp.	France	135	1.00
Staphylococcus aureus	US	1547	1.00
	UK	154	1.00
	France	504	0.50
S. aureus	US	461	1.00

[redacted] Resistant	UK	28	1.00
	France	147	0.50
S. aureus [redacted] Susceptible	US	1066	1.00
	France	219	0.50
S. aureus Erythromycin Resistant	US	372	1.00
	UK	24	1.00
	France	152	0.50
S. aureus Erythromycin Susceptible	US	717	1.00
	UK	65	0.50
	France	231	0.50
S. aureus MLS_BC	US	249	2.00
	UK	28	1.00
	France	167	1.00
S. aureus MLS_BI	US	11	1.00
	UK	31	0.50
	France	33	0.50
S. aureus MLS_BS	US	179	1.00
	UK	61	0.50
	France	139	0.50
Staphylococcus epidermidis	US	594	0.50
	UK	22	0.50
	France	30	0.25
S. epidermidis [redacted] Resistant	US	251	0.50
	France	123	0.25
S. epidermidis Erythromycin Susceptible	US	149	0.50
	UK	15	1.00
	France	231	0.50
S. epidermidis Erythromycin Resistant	US	177	0.50
	France	92	0.50
S. epidermidis MLS_BC	US	99	0.50
	France	78	1.00
S. epidermidis	France	30	0.25

MLS_BI

S. epidermidis	US	76	0.50	
MLS_BS	UK	15	1.00	
	France	112	0.25	
Staphylococcus haemolyticus	US	85	1.00	
	France	27	0.50	
Staphylococcus hominis	US	82	0.50	
	France	21	0.25	
Staphylococcus saprophyticus	US	61	1.00	
Staphylococcus simulans	US	26	0.50	
Staphylococcus warneri	US	35	1.00	
Coagulase-negative	US	605	1.00	
staphylococci	UK	50	1.00	
	France	112	0.500	

Summary and comments on Table 1 data (comments refer to US isolates unless otherwise noted):

The minimum concentration of Synercid required to inhibit 90% of the staphylococci was $\leq$1.0μg/mL if the resistant phenotype, MLS_BC was excluded. For isolates of *S. aureus* with the phenotype MLS_BC 90% were inhibited by $\leq$2.0μg/mL.

Ninety percent of the isolates of *S. agalactiae, S. pyogenes*, and *S pneumoniae* were inhibited by $\leq$1.0μg/mL of Synercid. It required $\geq$2.0μg/mL of Synercid to inhibit 90% of the other species of streptococci tested.

The minimum concentration of Synercid required to inhibit 90% of the *E. faecium* tested was $\leq$2.0μg/mL. If the vancomycin susceptible *E. faecium* and the VAN B types are excluded 90% of the isolates would be inhibited by $\leq$1.0μg/mL. Published studies have indicated $\leq$4.0μg/mL to inhibit 90% of *E. faecium*(20). The minimum concentration of Synercid in this study to inhibit 90% of vancomycin-susceptible *E. avium* was 2.0μg/mL while the MIC_{90} for vancomycin-resistant *E. avium* and other species of enterococci was $\geq$4.0μg/mL.

The data in Table 2 represents data submitted in June 1998. This data was part of a RPR presentation at a National Committee for Clinical Laboratory Standards (NCCLS)

meeting and was used by the NCCLS to establish breakpoints. This data contains isolate information in Table 1 to which supplemental isolate data was added since the original NDA submission. The data in Table 2 support the conclusions made from data in Table 1.

Table 2. Supplemental data (submitted 5/98) on activity (MIC_{90}) of Synercid against target organisms.

Organism	Number of Isolates	MIC_{90} (ug/mL)
Enterococcus faecium Vancomycin and multi-resistant	1305	1.00
E. faecium Vancomycin, teicoplanin and multi-resistant	895	1.00
E. faecium Vancomycin and multi-resistant, teicoplanin susceptible	304	1.00
Staphylococcus aureus	3598	1.00
S. aureus [redacted] multi-resistant	1051	1.00
S. aureus [redacted] susceptible	2140	1.00
Staphylococcus epidermidis	1760	0.50
S. epidermidis [redacted] multi-resistant	786	0.50
S. epidermidis [redacted] susceptible	940	0.500
Streptococcus agalactiae	221	1.00
Streptococcus pneumoniae	3036	0.50

S. pneumoniae Penicillin-susceptible	2072	0.50
S. pneumoniae Penicillin-intermediate	344	1.00
S. pneumoniae Penicillin and multi-resistant	329	1.00
Streptococcus pyogenes	928	0.25

PRE-CLINICAL - IN-VIVO

PHARMACOKINETICS

After single and repeated 7.5mg/kg iv doses, q8h or q12h, Synercid achieved an HPLC-

The AUC_8(µg•h/mL) for quinupristin and metabolites was 7.20 ± 1.24 and for dalfopristin and its metabolites 10.57 ± 2.24. The AUC_{24} being ~ 53µg•h/mL. For the q12 dosing regimen the AUC_{24} is ~34µg/mL.

In-vitro binding of quinupristin and dalfopristin to serum proteins was determined to be 55 to 78% and 11 to 26% respectively. Elimination of quinupristin and dalfopristin occurs primarily by fecal excretion, with 69% and 66% respectively of the single dose administered eliminated by 96 hours post-dosing. After seven days, 15% and 19% respectively was eliminated through the kidneys.

Penetration of either component of Synercid or RP 12536 into -alveolar lavage fluid **was not demonstrated** in healthy human volunteers. The applicant attributes this to technical problems related to handling the specimens before they were assayed and possibly the use of non-infected rather than infected human volunteers. The degree of penetration of Synercid into animal lung tissue was demonstrated. It was found that penetration into lung tissue did not increase proportionally to the dose.

Determination of serum bactericidal levels was not possible due to technical difficulties attributable to stabilization of the serum and use of 100% serum rather than 50% serum as usually done. The sponsor states that work is being done to optimize this procedure.

PHARMACODYNAMICS

The 24-hour cumulative dose or area-under-the-concentration vs time curve (AUC) or the amount of drug exposure was shown by two animal models to be the pharmacokinetic parameter that correlates best with the in-vitro activity of Synercid. The AUC_{24} equals ~ 53μg•h/mL with the AUC/MIC equaling 53 for a q8hr dose and ~34 for a q12hr dose.

Synercid was tested against a variety of target pathogens in discriminatory animal models of infection.

In rat and rabbit models of endocarditis induced by MLS_BS and MLS_BI strains of *S. aureus* Synercid when given at a dose of q8h(30mg/kg) IM reduced CFU/mL in vegetations by three to four log_{10}. However, this same dose of Synercid did not reduce the CFU/mL of MLS_BC strains of MRSA to the same extent even though in-vitro the organism was found to be susceptible. The explanation for this apparent discrepancy between the in-vitro and in-vivo findings was that each Synercid component displayed a different diffusion pattern as noted by autoradiography studies into the cardiac vegetation. Quinupristin, displayed a homogeneous diffusion whereas dalfopristin showed a decreased gradient of concentration between the periphery and the core of the vegetation(12, 24). This model was used to demonstrate the necessity of maintaining a consistent level of dalfopristin in such lesions in order to achieve bactericidal activity against bacteria.

In a rabbit model of vancomycin-resistant *E. faecium* induced endocarditis MLS_BI strains were associated with a decreased efficacy of Synercid.

TENTATIVE SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

MIC Breakpoints: Based on the pharmacokinetic profile of Synercid and in-vitro susceptibility testing of target pathogens provisional breakpoints of ≤1μg/mL indicating susceptibility, 2μg/mL for intermediate susceptibility, and ≥4μg/mL for resistant to Synercid were chosen for the clinical trials.

Disc provisional interpretive criteria: Based on the "error-rate bounded" method using the provisional MIC noted above two provisional disc interpretive criteria were determined for the 15μg Synercid disc:

[redacted]

Proposed zone diameter criteria (mm)			% Interpretive Error		
Susceptible	Intermediate	Resistant	Very Major	Major	Minor
≥19[a]	16-18	≤15	0.0	0.0	1.9
≥18[b]	ND	≤17	1.9	0.0	NA

[a] Based on: ≤1μg/mL = susceptible; 2μg/mL = intermediate; ≥4μg/mL = resistant
[b] Based on: ≤2μg/mL = susceptible; ≥4μg/mL = resistant
ND = Not determined
NA = Not applicable

CLINICAL EFFICACY

CLINICAL MICROBIOLOGY

Isolates - Relevance to Proposed Indications:

Complicated skin and skin structure infections: *Staphylococcus aureus* (including [redacted] resistant strains), *Staphylococcus epidermidis* (including [redacted] resistant strains), *Streptococcus agalactiae*, and *Streptococcus pyogenes* including cases associated with concurrent bacteremia with these microorganisms.

[redacted]

Infections due to vancomycin-resistant *Enterococcus faecium*, including cases associated with concurrent bacteremia.

Infections caused by *Staphyloccocus aureus* (including [redacted] susceptible and [redacted] resistant strains), in patients failing other therapies, including cases associated with concurrent bacteremia.

The above organisms, with the exception of *S. epidermidis* (including [redacted] resistant isolates) listed under "Complicated Skin and Skin Structure Infections", are clinically associated with the stated indications and in-vitro susceptibility test data

indicates that Synercid has activity against these organisms thus the indications\organisms combinations are appropriate for this antimicrobial.

CLINICAL TRIAL DATA

Overall Correlation of Therapeutic Data with Tentative MICs

Analysis by the sponsor of the treatment outcome data for "Complicated Skin and Skin Structure Infections", [redacted] "Systemic Infection with Vancomycin-Resistant *E. faecium*" using the provisional susceptibility breakpoints of: ≤1μg/mL = susceptible; 2μg/mL = intermediate; ≥4μg/mL = resistant revealed the following.

Complicated Skin and Skin Structure Infections

Two clinical phase 3 studies were conducted for "Complicated Skin and Skin Structure Infections". Both studies (JRV304 & JRV 305) were open design studies. Patients received Synercid in these studies at a dose of 7.5mg/kg IV Q12h for up to 14 days. The microbiology data from both of these studies were combined and analyzed by the company. The analysis provided by the company was reviewed for completeness and accuracy.

For " all pathogens excluding enteric gram-negative bacilli" (*Haemophilus* not excluded because there is one *Haemophilus parainfluenzae* in the data base) 67% (111/165) of those subjects who were bacteriologically evaluable had a satisfactory clinical response when the pathogen had an MIC of ≤2μg/mL whereas when the MIC of the pathogen was ≥4μg/mL there was a 44% (4/9) satisfactory response in the bacteriologically evaluable subjects.

A 67% (101/151) satisfactory clinical response rate was seen for MLS_BS/MLS_BI, MLS_BC, MS or MR stains of *S. aureus* (101/151) or coagulase-negative staphylococci (36/54) when the MIC was ≤1μg/mL in the bacteriologically evaluable and all-treated populations.

The overall satisfactory clinical response rates (cured plus improved) for Synercid and comparator treated patients at the Test-of-Cure visit for both trials combined were 68% vs 72% respectively. The overall bacteriologic satisfactory response rates (eradication plus presumed eradication) for Synercid and comparator-treated patients at the Test-of-Cure visit were 60% vs 73% respectively.

[redacted]

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Ninety-one percent (167/184) of the vancomycin-resistant *E. faecium* isolates had MICs of ≤1μg/mL. Approximately 72% (121/167) of the cases with these isolates had satisfactory pathogen responses and clinical responses. Only six (6) of 10 (60%) strains and 1 of 2 (50%) strains with MICs of 2 and 4μg/mL respectfully correlated with satisfactory pathogen and clinical responses.

Because of the very small numbers of organisms other than VREF*aecium* pathogen and clinical response is not evaluable.

Infections Caused by *Staphylococcus aureus*(including susceptible and resistant isolates)

Data for analysis was the combination of several studies. The number of *S. aureus* from bacteriologically evaluable patients under study protocols JRV304 (Complicated skin and skin structure infections), 305 (Complicated skin and skin structure infections), and 306 in the pathogen eradication response and clinical response analysis groups totaled 329. Data was analyzed by the company and reviewed for completeness and accuracy.

In the pathogen eradication analysis 135 (41%) were *S. aureus*, 23 (7%) were methicillin-resistant, 90 (27%) were methicillin-susceptible, 8 (2%) were MLS_BC, and 83 (25%) were MLS_BS and MLS_BI. Of the total *S. aureus* the 208 (63%) that were eradicated had a Synercid MIC of ≤1μg/mL. Of the 23 resistant *S. aureus* with a Synercid MIC of ≤1μg/mL 11 (48%) were eradicated.

In the clinical response analysis 113 (34%) were *S. aureus*, 23 (7%) were resistant, 85 (26%) were susceptible, 27 (8%) were MLS_BC and 81 (25%) were MLS_BS and MLS_BI. Of the 206 (63%) patients with *S. aureus* who clinically responded the Synercid MIC was ≤1μg/mL. Of the 23 patients with resistant *S. aureus* 10 (43%) clinically responded. The Synercid MIC for all the resistant *S. aureus* isolates was ≤1μg/mL. The success rate in the clinical response groups for the MLS_BC and the MLS_BS, MLS_BI groups were 26% (7/27) and 70% (57/83) respectfully. All the isolates in these three groups had Synercid MICs of ≤1μg/mL.

SUMMARY

Analysis of the therapeutic efficacy of Synercid for the treatment of "Complicated Skin and Skin Structure Infections", "Systemic Infection with Vancomycin-Resistant *E. faecium*" gave a satisfactory pathogen eradication and clinical response ~71% of the time when the MIC of the organisms was ≤1μg/mL in the bacteriologically evaluable patients. At MICs of ≤2μg/mL there was a satisfactory pathogen eradication and clinical response ~72% of the time in the bacteriologically evaluable populations in all clinical trials.. When the MIC of the

organism was ≥4μg/mL the satisfactory pathogen eradication and clinical response rates were ~39% and ~46% respectfully.

Overall Correlation of Therapeutic Data with Tentative Zone Diameters

Analysis by the sponsor of the treatment outcome data for "Complicated Skin and Skin Structure Infections" [redacted] "Systemic Infection with VREF*aecium*" using the provisional susceptibility disk diffusion interpretive criteria of ≥19mm = susceptible, 16-18mm = intermediate, and ≤15 = resistant revealed the following.

Complicated Skin and Skin Structure Infections

All pathogens excluding enteric gram-negative bacilli.

Satisfactory pathogen responses in bacteriologically evaluable patients:

Overall: ≥19mm = 70%; ≤15mm = 50%
S. aureus or coagulase-negative staphylococci (all types): ≥19mm = 65%

Satisfactory clinical responses in bacteriologically evaluable and all treated patients:

Overall: ≥19mm = 67%; ≤15 = 56%
S. aureus or coagulase-negative staphylococci (all types): ≥19mm = 65%

Use of the alternate disk diffusion criteria, ≥20mm = S; ≤16mm = R for both of the above gave similar correlation's in each respective case.

[redacted]

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

CONCLUSIONS AND RECOMMENDATIONS

The in-vitro data to support the provisional MIC breakpoints and disk diffusion zone size interpretation as well as the quality control and potential effects that variations in the pH, inoculum concentration etc. might have on susceptibility test results were adequately studied. For *Enterococcus faecium*, *Staphylococcus* spp. (excluding *Streptococcus pneumoniae*), , and *Streptococcus* spp. the provisional MIC breakpoints (≤1µg/mL = susceptible, ≥4µg/mL = resistant) seemed adequate to predict clinical outcome The provisional disk diffusion criteria of ≤15mm = resistant, ≥19mm = susceptible also seemed adequate to determine clinical outcome.

The following MIC breakpoints and zone diameter interpretive criteria are indicated for Synercid:

For testing *Enterococcus faecium*, *Staphylococcus* spp., and *Streptococcus* spp. (excluding *Streptococcus pneumoniae*).

	MIC (µg/mL)[a]	Zone diameter (mm)[b]
Susceptible	≤1.0	≥19
Intermediate	2.0	16 - 18
Resistant	≥4.0	≤15

a. The MIC interpretive criteria for *Streptococcus* spp. is applicable only to tests performed by the broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.

b. The zone size interpretive criteria for *Streptococcus* spp. is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood, incubated in 5% CO_2.

There are indications in the literature that the MIC breakpoints are not capable of separating various phenotypes of organisms (24). For instance the phenotypes MLS_B and MLS_BC both have MICs of $\leq 1\mu g$. The clinical significance of this is unclear, however, in the nosocomial clinical trials there was a significant difference in the cure rates of pneumonia caused by the MLS_B and MLS_BC phenotypes of *S. aureus* (72% vs 20% respectively. There was also noted in the animal endocarditis models a decreased efficacy of Synercid against MLS_BC strains of *S. aureus* and MLS_B strains used to induce endocarditis. It has been speculated that testing either of the compounds of Synercid may be able to discriminate these strains but no conclusive data exists to support this point. In the animal endocarditis models the AUC/MIC of quinupristin seemed a better predictor of efficacy (12, 24).

In-vivo animal data to study the pharmacokinetics and pharmacodynamics of the drug provided information that indeed the dalfopristin/quinupristin (Synercid) combination is not bactericidal against *E. faecium* and may not be bactericidal against certain strains of other organisms such as [redacted] resistant *S. aureus* with constitutive resistance to erythromycin (MLS_BC). Further work by the applicant in this area is needed to define whether the dosing is adequate and whether the 70/30 ratio of dalfopristin to quinupristin is appropriate.

Under **INDICATIONS AND USAGE** in the package insert a note indicating that the antimicrobial is not effective against *E. faecalis* has been added. In addition, the request to indicate that [redacted] resistant *S. epidermidis* can be treated with Synercid has been removed because of the small numbers of these organisms in the clinical therapeutic data.

Information as to the potential spread of Synercid resistant *E. faecium* as well as the potential spread of *E. faecalis* between hospitalized patients treated with Synercid was not presented in spite of the fact that the applicant noted in the submission that in deed their was this possibility. It has been suggested that in the package insert under precautions that a statement be made of this potential.

A number of organisms have been taken off of the second list. The majority of organisms have been excluded because there were less than 100 isolates for which susceptibility data was presented. In the case of *N. meningitidis*, and *N. gonorrhoeae* the organisms were removed because there are no meningitis or gonorrhea treatment claims being made for the antimicrobial.

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Proposed Synercid Package Insert

Microbiology: The streptogrammin components of Synercid, quinupristin and dalfopristin, [redacted] ratio of 30 parts quinupristin to 70 parts dalfopristin. These two components act synergistically so that Synercid's microbiologic in vitro activity is greater that that of the components individually. Quinupristin's and dalfopristin's metabolites also contribute to the antimicrobial activity of Synercid. In vitro synergism of the major metabolites with the complementary parent component has been demonstrated.

Synercid is bacteriostatic against *Enterococcus faecium* and bactericidal against [redacted] susceptible and resistant staphylococci.

The site of action of quinupristin and dalfopristin is the bacterial ribosome. Dalfopristin has been shown to inhibit the early phase of protein synthesis while quinupristin inhibits the late phase of protein synthesis. [redacted]

Synercid has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms
Enterococcus faecium (**Vancomycin-resistant and multi-drug resistant strains** [redacted] **only**)
Staphylococcus aureus ([redacted] susceptible strains only)
Streptococcus pyogenes

NOTE: Synercid is **not active** against *Enterococcus faecalis*. Differentiation of enterococcal species is important to avoid misidentification of *Enterococcus faecalis* as *Enterococcus faecium*.

The following in vitro data are available, **but their clinical significance is unknown.**
The combination of quinupristin and dalfopristin (Synercid) exhibits in vitro minimum inhibitory concentrations (MICs) of $\leq$1.0µg/mL against most ($\geq$90%) of isolates of the following microorganisms; however the safety and efficacy of Synercid in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Aerobic gram-positive microorganisms
Staphylococcus aureus (methicillin-resistant strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
[redacted]
Streptococcus agalactiae

SUSCEPTIBILITY TESTING:

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of microorganisms to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution[1] method (broth or agar) or equivalent using standardized inoculum concentrations, and standardized concentrations of quinupristin/dalfopristin (Synercid) in a 30:70 ratio made from powder of known potency. The MIC values should be interpreted according to the following criteria:

FOR SUSCEPTIBILITY TESTING OF *ENTEROCOCCUS FAECIUM*, *STAPHYLOCOCCUS* SPP., AND *STREPTOCOCCUS* SPP. (excluding *Streptococcus pneumoniae*)[a]

MIC (µg/mL)	Interpretation
≤1.0	Susceptible(S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

[a] The interpretive values for *Streptococcus* spp. are applicable only to broth microdilution susceptibility testing using cation-adjusted Mueller-Hinton broth with 2 - 5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the concentration of the antimicrobial compound in the blood reaches usually achievable levels. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control

A standardized susceptibility test procedures requires the use of laboratory control organisms to control the technical aspects of the laboratory procedures. Standard quinupristin/dalfopristin powder in a 30:70 ratio should provide the following MIC values with the indicated quality control strains:

Microorganism (ATTC®#)	MIC Range (µg/mL)
Enterococcus faecalis (29212)	[redacted]
Staphylococcus aureus (29213)	

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15µg quinupristin/dalfopristin in a ratio of 30:70 (Synercid) to test the susceptibility of microorganisms to quinupristin/dalfopristin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15µg quinupristin/dalfopristin disk should be interpreted according to the following criteria:

FOR SUSCEPTIBILITY TESTING OF ENTEROCOCCUS FAECIUM, STAPHYLOCOCCUS SPP., AND STREPTOCOCCUS SPP.(excluding *Streptococcus pneumoniae*)[b]

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
16 to 18	Intermediate (I)
≤15	Resistant (R)

b. The zone diameters for *Streptococcus* spp. are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood when incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for quinupristin/dalfopristin.

Quality Control

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique the 15µg quinupristin/dalfopristin (30:70 ratio) disk should provide the following zone diameters with the quality control strains listed below:

Microorganism (ATCC® #)	Zone Diameter Range (mm)
Staphylococcus aureus (25923)	23 to 29

[redacted]

ATCC® is a registered trademark of the American Type Culture Collection

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2. NCCLS, *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Sixth Edition; Approved Standard. NCCLS document M2-A6 (ISBN 1-56238-308-6). See above for address.

PRECAUTIONS:

[redacted]

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA#: 50-748 **REVIEW #1** **REVIEW DATE: 7/30/98**

[redacted]

Drug interactions:

In vitro combination testing of Synercid with aztreonam, cefotaxime, ciprofloxacin, doxycycline, gentamicin, [redacted], against Enterobacteriaceae and *Pseudomonas aeruginosa* did not show antagonism.

[redacted]

/S/ 8/27/98
Frederic J. Marsik, Ph.D.
Review Microbiologist

cc: Original 50-748
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