incidence was comparable in all 3 groups, with rates of 20.6% for the normal group, 25.3% for the moderately elevated group, and 16.5% for the 2x ULN group. .

Six clinical liver dysfunction events considered to be probably or possibly related to drug occurred in the comparative studies: 3 in the Synercid group and 3 in the comparator group. In the Synercid group, there was one report each of hepatitis, jaundice and cholestatic jaundice. In the comparator group, there was one case of hepatitis and two of cholestatic jaundice. None of these reports led to treatment discontinuation.

There were no deaths related to a hepatic dysfunction adverse event.

Reviewer's Comment: These data do not establish a pattern of hepatic toxicity due to Synercid use which is markedly different from that seen in the comparator drugs. Synercid use is associated with increases in total and conjugated bilirubin more frequently than seen with the comparator drugs.

6. Conclusions

As noted above, Synercid is associated with more adverse events than the comparator drugs especially in the area of discontinuations due to adverse events. About 19% of the Synercid patients discontinued due to these events, as compared to 6.3% of patients taking the comparator drugs. Synercid also causes increases in total and conjugated bilirubin, although the clinical significance of this phenomenon is unclear and appears reversible.

From a safety viewpoint, a decision to approve Synercid in these "standard" indications should consider the likelihood of a higher rate of adverse events vs. the potential benefit of the drug in a potential patient population.

/S/
David Bostwick

/S/ 8-19-98
Rosemary Roberts, M.D.

Orig NDA
HFD-340
HFD-520
HFD-520/DepDir/Gavrilovich
HFD-520/Clin/Rakowsky
HFD-520/Clin/Thompson
HFD-520/Clin/Bostwick
HFD-520/TClin/Roberts
HFD-520/Proj Mgr/Dillon-Parker
HFD-520/Micro/Marsik
HFD-520/Chem/Timper
HFD-240

Concurrence Only:
HFD-520/DivDir/Chikami
/S/ 8/21/98

EMERGENCY USE STUDIES/VREF INDICATION

1. **Rationale for Development:**
   a. *In vitro* activity: Synercid is an injectable streptogramin, a class of antimicrobials belonging to the macrolide-lincosamide-streptogramin (MLS) family of antibiotics, with its target of activity being the ribosome of susceptible bacteria. Synercid exhibits activity against *Streptococcus pneumoniae* and other aerobic members of the streptococcal family, *Staphylococcus aureus* and other staphylococci, *Moraxella catarrhalis*, *Haemophilus influenzae*, and atypical pathogens such as *Chlamydia* spp., *Legionella* spp., and *Mycoplasma* spp. In addition, the agent appears to be active against *Enterococcus faecium*, including most glycopeptide-resistant strains.
   b. Medical Need: At the time of the initial IND submission in December, 1991, the applicant was not intending to develop Synercid for the treatment of infections due to *Enterococcus faecium*, specifically vancomycin-resistant strains (VREF). However, a sharp rise in the United States in both the number of nosocomial infections due to *Enterococcus faecium* and in the proportion of strains of this pathogen found to be vancomycin-resistant, led to increasing requests for the emergency use of Synercid. *Enterococcus faecium* is inherently resistant to multiple classes of antimicrobials, and many clinical VREF strains were found to be resistant to the three traditionally utilized classes of antimicrobials used to treat infections due to this pathogen, namely the aminoglycosides, penicillins, and glycopeptides (specifically vancomycin).
   c. Subpart E Development: On May 4, 1994, a meeting was held between representatives of Rhone-Poulenc-Rorer and DAIDP to discuss the suitability of a Subpart E development program for the use of Synercid in the treatment of VREF infections. A study was submitted on May 20, 1994, and reviewed by DAIDP. This study (Study 301) was initiated on October 24, 1994. A detailed discussion of this study, and all subsequent studies that have their design based upon the Study 301 protocol will follow.

2. **Outline of Studies Submitted**: Four VREF studies were submitted as part of NDA 50-747, namely studies 399, 301, 398A (also referred to as 398) and 398B. While the large majority of patients were enrolled due to a VREF infection, all studies but Study 301 allowed for enrollment of patients with other gram-positive infections.
   a. Study 399: "Synercid for Emergency Use". This was a collection of the emergency INDs requesting the use of Synercid. Data were collected on 227 patients at 159 sites in 6 countries (Belgium, France, Israel, Italy, United Kingdom and United States) who received Synercid from March 20, 1993 to August 10, 1995. The amount of documentation both required and actually submitted by the individual investigators was highly variable. The dose of Synercid utilized in the majority of cases was 7.5 mg/kg/dose q 8 hours, with a smaller percentage receiving a dose of 7.5 mg/kg q 12 hours.

b. Study 301: "Study of the Treatment of Infections Due to Vancomycin-resistant *Enterococcus faecium* (VREF) with Synercid". This was a prospectively designed study conducted from October 24, 1994 to February 22, 1996, enrolling 265 patients at 44 study centers in the United States. This study required rigorous documentation by the investigator and the study centers were prospectively identified. Patients were treated with Synercid at 7.5 mg/kg q8 hrs. Patients were to be evaluated at an end-of-treatment (EOT) and test-of-cure (TOC) follow-up, with the time to the TOC visit determined by the infection site being treated, consistent with FDA/IDSA guidelines for that specific infection site.

c. Study 398 (398A): "Open Study of Synercid for Emergency Use (Infections Due to Resistant Bacteria, Treatment Failure or in Treatment-intolerant Patients)". This study was conducted from May 17, 1995 to March 8, 1996, and enrolled 219 patients at 145 study centers in 6 countries (Canada, France, Germany, Israel, United Kingdom and United States). This study was a continuation of Study 301 and the study protocol was similar. As with Study 301, rigorous documentation and follow-up evaluation were prospectively defined by the protocol. The dose of Synercid was 7.5 mg/kg either q8 or q12 hrs. with the length of therapy determined by the investigator.

d. Study 398B: "Open Study of Synercid for Emergency Use (Infections Due to Resistant Bacteria, Treatment Failure or in Treatment-intolerant Patients)". This study was conducted from January 2, 1996 to December 5, 1996, and enrolled 528 patients at 267 study centers in 6 countries (France, Israel, Italy, Sweden, United Kingdom and United States). Patients were to be followed up to the EOT, with a TOC visit recommended but not as strictly required as in Study 301. Investigators were required to complete detailed case report forms, but unlike studies 301 and 398, were not required to write an overall patient summary (whose purpose was to clearly summarize the case with emphasis on the infection being treated and on the investigator's final impression regarding the efficacy and safety of Synercid). The dose was the same as used in Study 398.

e. Differences in Studies: There are several major differences among the 4 studies:

   1. Prospective vs. Retrospective: Study 399 was a collection of the initial Emergency INDs with the investigator submitting final patient reports, with vital patient information, a period of time after drug use completion. The other 3 studies (301, 398, and 398B) were prospective.
   2. Documentation Required: While studies 301, 398 and 398B all had similar Case Report Forms (CRFs) the actual details required were more variable in Study 398B, with several sections of the CRF titled "optional".
   3. Documentation Received: Study 301, with the study centers prospectively identified and with a strong emphasis placed on the investigators to complete the detailed CRFs, had the most consistent

amount of documentation of the 4 studies. In addition, in Study 301, investigators were asked to write a patient summary which would provide an overall assessment of the patient's case in regard to the VREF infection and to the potential impact of Synercid use. These summaries were submitted by nearly all of the investigators in Study 301. Study 398 had a larger number of study centers, with these centers being enrolled on an emergency use basis (i.e., the study center asked the sponsor to be enrolled in the study, the reverse of the situation in Study 301). While the CRFs used in this study were identical to those used in Study 301, the actual amount of documentation was more variable. In addition, though strongly encouraged, patient summaries were either not written or written with little detail in a large percentage of patients. Study 398B had even more variable levels of documentation.

3. **Study Design Issues:**
   a. Dosing Regimens: The length of therapy was not specified in the study protocols, but was to be determined by the individual investigators. The dose to be administered was to be 7.5 mg/kg/dose either q 8 or q 12 hrs., depending on the severity of illness, with the q 8 hr dosing schedule expected to be the more commonly used.
   b. Endpoints: Because VREF infections are not homogenous, but a collection of various sites of infection where VREF is the pathogen, establishing specific endpoints which could be applied to all enrolled patients was not felt to be feasible. At the Subpart E meeting (May 4, 1994) it was, therefore, agreed that IDSA/FDA guidelines would be used for each site of infection (e.g., patients with a VREF infection involving the intra-abdominal area would be analyzed using criteria already developed for this site of infection). Mortality, though considered to be an important parameter to follow, was not felt by the applicant to be an appropriate endpoint because of multiple comorbidities in the patient population which would contribute to the overall mortality rates.
   c. Specific Endpoints: As shown in the table below (obtained from page 44 of the Study 301 final study report) different primary efficacy variables were chosen for each specific indication. The primary endpoint, as chosen by the applicant, is the one underlined for each indication in the table below.

Summary of Efficacy Variables Analyzed for each Indication

Indication	Efficacy Variable			
	Clinical Response	By-pathogen Bacteriologic Response	By-patient Bacteriologic Response	Overall Response
Bacteremia of unknown source	Secondary	Secondary	Primary	Secondary
Central catheter-related bacteremia	Secondary	Secondary	Secondary	Primary
Endocarditis	Secondary	Secondary	Secondary	Primary
Intra-abdominal infection	Secondary	Secondary	Secondary	Primary
Skin and skin structure infection(s)	Primary	Secondary	Secondary	Secondary
Urinary tract infection	Secondary	Secondary	Secondary	Primary
Bone and joint infection	Secondary	Secondary	Secondary	Primary
Respiratory tract infection	Secondary	Secondary	Secondary	Primary
Deep wound other than intra-abdominal	Primary	Secondary	Secondary	Secondary
Intravascular site infection	Secondary	Secondary	Secondary	Primary

4. **Issues Raised/Considered Prior to Analysis of Patient Data:**
Several important issues needed to be addressed before the medical officer could start the analysis of the patient data.

a. Site-specific versus organism-specific analysis: The Division of Anti-Infective Drug Products has based approval on the ability of an agent to treat infections at a specific infection site, and usually not upon the activity of an agent against a specific pathogen. Indications are specified by site of infection (such [redacted] with pathogens relevant to each infection site listed under the specific indication (e.g., for the above listed indications, *Streptococcus pneumoniae* would be listed as a pathogen). The primary emphasis of data analysis is to show that an agent can, in an overall context, treat infections at a given site.

The VREF studies enrolled patients with a specific organism (note, that studies 398, 398B, and 399 did allow for enrollment of patients with other gram-positive pathogens, but the major emphasis continued to be enrollment of patients with VREF), which may have been a pathogen at one of many sites of infection. The medical officer broke each study down into individual sites of infection, and then established evaluability and efficacy criteria for each specific site of infection using IDSA/FDA guidelines. When these criteria differed from those used by the applicant (as outlined in the study protocols) the medical officer noted the rationale for the differences. The medical officer analyzed the patients per site of infection, with the final conclusion about each study to be based upon a pooling of these results.

b. Control Group: At the May 24, 1994 meeting, the division strongly stressed that if the applicant chooses to use non-comparative studies as their support for subsequent approval of Synercid for the treatment of VREF infections,

then a well established and documented historical control would be needed. At that time, it was presumed that an adequate historical control could be established and that the results from the VREF studies could be analyzed in light of this control. However, studies in the literature have employed different treatment regimens, endpoints, definition of disease, and patient populations. This has made assessment of the historical response in regard to both mortality and resolution of infection at specific sites difficult.

c. Population Enrolled: The patient population enrolled had multiple concomitant medical problems and medications. In addition, the overall mortality rates for each study were high. These factors made assessment of the response rates especially problematic in these studies which did not have a concurrent control.

d. Bacteremia of Unknown Origin: A large percentage (close to 25% in each of the 4 studies) of patients were enrolled under the category of "bacteremia of unknown origin", an indication not recognized by this division. Due to a lack of IDSA/FDA guidelines and lack of clarity in the study protocols in regard to evaluability and efficacy criteria for these patients, the medical officer developed strict criteria after reviewing the literature.

e. Adequacy of Documentation: While studies 301, 398, and 398B were prospectively designed treatment studies, the level of documentation varied considerably among these studies. For studies 301 and 398, there was significant emphasis placed on adequate documentation and on the completion of the CRFs (case report forms). Similar CRFs were used in Study 398B, but the adequate completion of these was not stressed, leading to a large number of patients being found unevaluable by the medical officer due to a lack of adequate information upon which to make a decision. Study 399 was essentially a series of emergency IND requests, and considering the nature of emergency INDs, adequacy of documentation was an issue with this study as well. Thus, the medical officer's final conclusions will be based upon data from the two well-documented, prospective studies, namely studies 301 and 398.

5. **General Inclusion/Exclusion/Evaluability Criteria** (as per the applicant):
Inclusion Criteria: Patients must have met all of the following conditions:

- Signed written informed consent form before any protocol-specific procedure
- Age 18 years or older with VREF infection presumed to be susceptible to Synercid

- Either a male or a non-pregnant, non-lactating female, who was using effective birth control (total abstinence, oral contraceptives [birth control pills], Norplant, or an intrauterine device) before, during and in the four weeks following the study
- For all women of child-bearing potential, laboratory serum pregnancy test was to be negative at baseline
- Documented infection with VREF, defined as *Enterococcus faecium* with intermediate susceptibility or resistance to vancomycin (disk diffusion zone size of ≤16 mm or MIC ≥8 μg/mL)
- Pathogen resistant to or having intermediate susceptibility to all available clinically appropriate antibiotics
- Documented intolerance or absolute contraindication to all available clinically appropriate antibiotics
- Documented infection (not colonization) with VREF that met the standard medical definition for that particular infection. Patients with more than one site of infection could qualify for more than one of the following categories (*Medical Officer Note: Specific sites of infection will be discussed later.)*

Medical Officer's Comments: The medical officer used these criteria with no changes.

Exclusion Criteria: Patients were not eligible for study participation if they presented with any of the following:

- Underlying disease with expected survival less than one week (except morbidity due to infectious process)
- Known hypersensitivity to streptogramin antibiotics (pristinamycin, virginiamycin, Synercid)

Medical Officer's Comments: In addition to these two criteria, the medical officer also found any patient previously enrolled into a VREF study to be unevaluable. This criterion affected approximately 5 patients per study.

It should be noted that the first exclusion criterion was rather loosely used due to the emergency IND nature of these studies. As will be seen, a large proportion of the patients who died did so during the first week of therapy.

Evaluability Criteria: In order to be found clinically evaluable, patients needed to fulfill the following criteria:

- Have had a documented infection with VREF, defined as *Enterococcus faecium* with an I or R susceptibility test result to vancomycin (disk zone 16 mm or less, MIC 8

µg/mL or more), with pathogen isolated any time prior to, or within 2 days of the start of Synercid.

- Have received at least 5 days of Synercid treatment
- Have received a mean daily dose of 15 mg/kg/day
- Not have received more than one course of Synercid therapy during the study
- Not have missed 10% or more doses
- Not have missed ≥1 dose on 3 consecutive days
- Have completed either the following Test-of-cure procedures or, in the case of a patient who discontinued study treatment, the End-of-treatment procedures:

  Required End-of-treatment procedures for clinical evaluability included:

  - Assessment of clinical signs and symptoms within the time frame of 1 day prior to the last dose and 2 days after the last infusion of study drug

  Required Test-of-Cure procedures for clinical evaluability included:

  - Assessment of clinical signs and symptoms between Day 3 and Day 21 after the last infusion of study drug
  - No missing clinical data, except if the available information clearly indicated Failure
- Two positive blood cultures obtained within 7 days prior to, or 2 days after, initiation of therapy were required for bacteremia of unknown source.
- Have met the specific inclusion criteria for each type of infection as will be described.

To be bacteriologically evaluable, patients must have been clinically evaluable and must have met the following criteria:

- Bacteriological specimens had to establish the diagnosis within the time frame of 96 hours prior to the day of the first dose of Synercid to Day 2 of therapy. Bacteriologic data were reviewed to ensure that positive cultures were from the indication-specific site and that there was no clear reversion to a culture-negative status prior to enrollment.
- Test-of-cure procedures had to be completed such that the bacteriological response could be assessed. Cultures obtained within 3 days prior to or after the Clinical Response Assessment were used. If there was more than one culture result within that time frame, all results were reviewed to ensure no discordance.
- For patients with VREF infection susceptibility testing had to be performed to other "long-term" (>20% of Synercid dosing days) presumed effective concurrent antibiotics used in the patient and *in vitro* resistance to those antibiotics had to be

confirmed. When susceptibility results were not available for an antibiotic received, the patient was non-evaluable if chloramphenicol or doxycycline was received for >20% of Synercid dosing days. The patient was evaluable for all other antibiotics received.

- The patient did not receive other effective antibiotic therapy on more than 20% of the days between the End-of-treatment and Test-of-cure Assessments. When susceptibility results were not available for an antibiotic received, the patient was non-evaluable if chloramphenicol or doxycycline was received.

Medical Officer's Comments: In regard to the evaluability criteria, the medical officer differed from the applicant in the following ways:

1. *Fully Evaluable: For reasons stated previously, a fully evaluable population was analyzed by the medical officer, with no separate "clinically evaluable" subset.*
2. *Length of Therapy: In order to be considered evaluable, the applicant required completion of at least 5 full days of therapy, while the medical officer used 3 full days, as traditionally done by this division.*
3. *Time to Test-of-Cure Visit: The medical officer chose 5 days, while the applicant used 3 days. The use of 5 days is more consistent with the various guidelines for the specific sites of infection studied in these trials. Additionally, a longer period of time off of drug was deemed as necessary in order to more clearly establish if Synercid truly played a role in patients with multiple concomitant medications/therapies/ conditions.*
4. *Concomitant Antimicrobials: The applicant used a cut-off of 20% of the study drug administration period as the criteria for finding a patient unevaluable due to use of an effective concomitant antimicrobial. The medical officer was more strict, finding any patient who received greater than 24 hours of an effective antimicrobial at any time during the study period (i.e., including pre-therapy, during therapy, and post-therapy up until the TOC visit) to be unevaluable.*

In addition to the changes listed above, the medical officer added two more general evaluability criteria:

1. Patients were found unevaluable if they did not have standard of care procedures performed. These included:

a. Surgical drainage of an abscess or similarly infected collections of fluid;
b. Appropriate debridement of infected tissue or bone;
c. Removal of infected hardware, except in cases where the goal of antibiotic therapy was to avoid such removal (will be discussed in more detail below);
d. Intraabdominal leakage due to anastomosis breakdown, biliary duct leakage, etc.

2. Patients that died of multi-organ failure while on therapy with neither documented persistence of VREF infection nor clinical suspicion on the part of the primary investigator that VREF infection led to the patient's demise were to be called unevaluable."

6. **Specific Evaluability/Efficacy Criteria:**

In the study protocol for Study 301 (with the same criteria used in study protocols for studies 398 and 398B), specific evaluability criteria were defined for 5 sites of infection: central catheter-related, endocarditis, intra-abdominal, skin and skin structure and urinary tract. Patients who did not qualify for any of the above 5 categories were considered candidates for participation in the studies under the "Other" category, if general inclusion/exclusion criteria were met first. As stated in the protocol:

"Bacteremia of unknown origin was to include at least one positive blood culture for the causative pathogen. Bacteremia of an unknown source was defined as bacteremia without an identifiable primary source of infection at the time of study entry.

- Types of infections included, but were not limited to, osteomyelitis, intravascular site, [redacted] deep wound other than abdominal, or febrile neutropenics.
- Central nervous system (CNS) infections could be treated at the discretion of the investigator. The diffusion of Synercid into cerebrospinal fluid had not been studied. At the time of the study, no suggestions could be made regarding the optimal treatment of CNS infections.
- This category was to allow for the collection of meaningful data on patients who would be treated with Synercid anyway.

"Note: Fever was defined as rectal temperature >38° C or oral temperature >37.5° C on two or more occasions during a 12-hour period.

"Authorization for treatment by Rhône-Poulenc Rorer was required for patients with a documented VREF infection (which included a positive culture and signs and symptoms of infection) who did not meet the inclusion/exclusion criteria for one of the five defined infection types but who qualified for treatment under the 'other' category."

Medical Officer's Comments: Specific efficacy criteria were not defined for any of the 11 categories of infection, with the study protocols stating: "The investigator assessed the absence or presence of signs and symptoms specific for each type of infection for clinical evaluation at baseline...Signs and symptoms were to be reassessed by the investigator at End-of-treatment, Test-of-cure, Follow-up and Late Follow-up (if applicable) and rated by comparison with baseline signs and symptoms..."

While specific evaluability criteria were not defined for the "other" categories of infection, and specific efficacy criteria and timing of the post-therapy evaluations were

also not defined in the study protocol for any of the 11 categories, the investigators were advised (in the "Investigator's Brochure") to refer to the IDSA/FDA guidelines when determining evaluability and efficacy.

In this section both the applicant's and medical officer's specific evaluability and efficacy criteria for each of the 11 "categories" of infection will be presented. Please note that general evaluability criteria were to be met as a pre-requisite. The final study reports submitted by the applicant used the term "Other" as an actual site of infection, as will be seen.

This section will first present the five categories for which specific evaluability criteria were defined (central-catheter-related infections, endocarditis, intra-abdominal infections, skin and skin structure infections, and urinary tract infections) and then present the remaining 6 in alphabetical order.

Both the evaluability criteria and efficacy criteria used by the medical officer followed the IDSA/FDA guidelines. In situations where divisional policy has differed from these guidelines (such as with urinary tract infections and accepted colony counts), the medical officer used divisional precedence. For bacteremia of unknown origin, the medical officer developed evaluability and efficacy guidelines after a literature review was completed.

a. Central Catheter-Related Bacteremia: Patients were to have met all of the following four criteria in order to be found evaluable:

   - Presence of a percutaneous inserted or tunneled central venous or arterial catheter
   - At least one of the following three criteria of no other apparent origin than a catheter infection: fever or hypothermia (<35.6°C) observed on two or more occasions over a 12-hour period, chills, leukocytosis with $>10^{10}$ PMN/L (10,000 PMN/mm^3), unless patient was neutropenic
   - One or more blood cultures positive for VREF with no apparent source other than the catheter
   - If catheter was removed prior to treatment, semi-quantitative catheter culture positive (>15 cfu, "Maki technique") with isolation of an identical causative pathogen from the catheter and from the bloodstream

- In order to be found cured, patients needed to have at least one negative blood culture at the EOT visit, with additional cultures at the TOC visit to be done at the investigator's discretion.

Medical Officer's Comments: In addition to the four evaluability criteria listed above, the medical officer also required that in situations where the catheter was removed prior to the initiation of Synercid, at least one positive blood culture was needed after removal to document persistence of infection.

In order to be found cured, the medical officer used the following criteria:

a. Documented negative blood cultures for two consecutive days and at the follow-up visit
b. No focus of infection developed during therapy suggestive of "seeding" with VREF
c. If the catheter was NOT removed prior to therapy, then removal during therapy was seen as a failure.

The last efficacy criterion can be viewed as controversial. However, the investigator brochure stressed that in biofilm studies Synercid appeared to be active in eradicating pathogens such as Staphylococcus species, and the investigators commonly stated in their summaries that the ultimate goal of therapy was to prevent catheter removal. Only a small number of patients were found to be failures due to this criterion, with one patient each in Study 301 and Study 398.

b. Endocarditis: Patients had to have met criteria for either definite, probable or possible endocarditis in order to be enrolled and found evaluable:

Definite endocarditis

- Culture of a valvular vegetation, of a vegetation that had embolized, or of an intracardiac abscess positive for VREF

Probable endocarditis

- Either persistently positive blood cultures and one of the following criteria: new murmur due to valvular insufficiency or predisposing heart disease and vascular phenomena

- Or intermittently positive blood cultures (i.e., not meeting definition for persistently positive), and all of the following criteria: fever, new regurgitant murmur or echocardiographic evidence of endocarditis, and vascular phenomena

Possible endocarditis

- Either persistently positive blood cultures and one of the following criteria: predisposing heart disease or vascular phenomena, or intermittently positive blood cultures (i.e., not meeting definition for persistently positive), and
- All of the following criteria: fever, predisposing heart disease, and vascular phenomena

The definitions of terms are:

- Blood cultures: at least 2 cultures of samples of ≥10 mL of blood each, drawn from two different access sites following application of antiseptic solution, with at least 5 minute (preferably 15-30 minutes) intervals between drawings
- Persistently positive blood cultures: all of 2, all of 3, or more than 66% of >3 cultures of separate blood cultures positive for the causative pathogen
- Vascular phenomena: petechiae, conjunctival hemorrhages, Roth's spots, Osler's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, pulmonary, coronary or peripheral emboli
- Predisposing heart disease: definite valvular or congenital heart disease or a cardiac prosthesis excluding permanent pacemakers

In order to be found cured, the patient was required to have negative cultures at the endpoints outlined in the Points-to-Consider Document and in the IDSA/FDA guidelines.

Medical Officer's Comments: The medical officer tried to simplify the evaluability criteria used by the applicant, and used the following:
In order to be evaluable, the patient needed the following:

a. Persistently positive blood cultures with no other apparent focus of infection
b. Echocardiogram (transesophageal or TEE) consistent with vegetations
c. If no TEE evidence, then patient needed a history of a predisposing condition AND either vascular phenomenon (Janeway lesions, Roth's spots, Osler's nodes, etc.) OR acute changes on cardiac auscultation.

The medical officer agreed with the applicant that follow-up blood cultures at 3 and 6 months were required. The specific efficacy criteria used by the medical officer were:
In order to be considered a cure, the patient needed the following:

a. Three consecutive blood cultures, drawn on different days, with no growth of VREF
b. Clearance of vegetation on TEE re-examination
c. Clearance of vascular phenomenon

Repeat cultures at 3 and 6 months post-therapy negative for VREF growth as well.

It should be noted that any patient who died secondary to endocarditis or related complications was to be considered a failure.

c. Intra-Abdominal Infections: In order to be found evaluable, patients were to have met all of the following three criteria:

- Radiological evidence (such as a CT scan or ultrasound) of intra-abdominal infection or at least one of the following: abdominal wall rigidity (localized or diffuse), mass or ileus
- Evidence of systemic inflammatory response (except if patient was neutropenic), i.e., at least one of the following: fever, elevated WBC count, hypotension, tachycardia, tachypnea, hypoxia or altered mental status
- Culture of intra-abdominal fluid or abdominal soft tissue positive for VREF.

In order to be found cured, the patient was required to have either a negative culture at the TOC visit (3 days or more post-completion of therapy) or a clinical picture consistent with a bacteriologic eradication and no source for culture available.

Medical Officer's Comments: The medical officer used the same evaluability criteria. In regard to the efficacy criteria, the medical officer used 5 days as the minimum amount of time post-therapy, and other criteria used were:

a. Appropriate surgical drainage of infectious process and repair of leakages (such as an anastomosis site leakage) were required. In situations where this was not the case, persistence of VREF was NOT seen as a study drug failure
b. Appropriate concomitant antibiotics for the treatment of other pathogens found in the cultures were required. Note, use of agents active against VREF, *in vitro*, would disqualify a patient.
c. Clinical improvement and either negative cultures or lack of a culturable infection site at the TOC visit.

Except for situations where further surgical therapy was seen as expected, subsequent surgery would be seen as a drug failure.

d. Skin and Skin Structure Infections: In order to be found evaluable, patients were to have met both of the following two criteria:

- Seropurulent drainage or at least three of the following: tenderness to palpation, erythema, induration, fluctuance
- Properly collected culture of drainage or material biopsied or aspirated from the site of infection positive for VREF

If drainage was present, a swab was to be used to obtain a sample. Precautions were to be taken not to touch the swab to surrounding skin or other potentially contaminated sites.

If aspiration was performed, the sample area was to be cleaned with alcohol or equivalent solution and allowed to dry prior to aspiration. If no fluid was obtained, 0.1 mL of non-bacteriostatic saline could be injected, reaspirated and submitted for culture.

In order to be found a cure, patients must have been considered clinically cured or improved by the investigator at the TOC visit.

Medical Officer's Comments: The evaluability criteria used by the medical officer were the same as those utilized by the applicant. However, since the medical officer analyzed fully evaluable patients only for efficacy, the definition of cure included either the lack of growth of initial pathogen on a repeat culture done at the TOC visit (defined as being at least 5 days after the completion of therapy) or no material available to culture.

e. Urinary Tract Infections: In order to be found evaluable, patients were to fit into one of the following four groups:

Acute Uncomplicated UTI

Patients were to have met all four of the following criteria:

- At least two of the following symptoms: dysuria, urgency, frequency, suprapubic pain
- No urinary symptoms in the four weeks prior to the current episode
- Positive leukocyte esterase (unspun urine) unless neutropenic
- Midstream urine culture growing at least 10^3 cfu/mL of VREF in unspun urine

Acute Uncomplicated Pyelonephritis

Patients were to have met all five of the following criteria:

- Fever, chills, flank pain
- Other diagnoses excluded
- No history or clinical evidence of urological abnormalities
- Positive leukocyte esterase (unspun urine) unless patient was neutropenic
- Midstream urine culture growing at least 10^4 cfu/mL of VREF in unspun urine

Complicated UTI and UTI in men

Patients with complicated UTI were to have met all four of the following criteria / UTI in men had to have met at least the last three criteria:

- At least one of the following factors associated with complicated UTI: presence of an indwelling or intermittent urinary catheter, >100 mL of residual urine retained after voiding, obstructive uropathy due to bladder outlet obstruction, a calculus or other causes, vesico-ureteral reflux or other urologic abnormalities including surgically created ileal loops, azotemia due to intrinsic renal disease, or renal transplantation
- At least two of the following symptoms (unless the patient was catheterized or was otherwise physically unable to exhibit the following symptoms): dysuria, urgency, frequency, suprapubic pain, fever, chills, or flank pain
- Positive leukocyte esterase (unspun urine) unless patient was neutropenic
- Midstream urine culture growing at least 10^5 cfu/mL of VREF in unspun urine for a Complicated UTI patient or 10^4 cfu/mL of VREF for a patient for a UTI in Men category or a specimen taken directly from the catheter growing at least 10^2 cfu/mL of VREF for catheter associated UTI

Asymptomatic Bacteriuria

Patients were to have met all three of the following criteria:

- No symptoms of UTI infection
- Positive leukocyte esterase (unspun urine) unless patient was neutropenic
- Two consecutive midstream urine cultures growing at least 10^5 cfu/mL of VREF in unspun urine >24 hours apart

A patient was considered a cure if the patient had both a clinical and bacteriologic cure/improvement (specifics not listed in the study protocols) at the TOC visit.

Medical Officer's Comments: The medical officer used the following evaluability and efficacy criteria for all categories of UTI:

In order to be evaluable, patients needed the following:

a. Urine culture (either clean catch or via catheter) with >10^5 cfu/mL of VREF was needed.
b. Urinary symptoms in patients capable of sensing this (i.e., in patients with indwelling catheters, frequency, burning, urgency, etc. would not be expected)
c. Positive leukocyte esterase (on unspun urine dipstick), unless the patient was neutropenic
d. Pure growth of VREF in culture.

In order to be found cured, the patient needed the following:

a. Less than or equal to 10^3 cfu/mL of VREF on repeat urine culture done at the TOC visit
b. Leukocyte esterase negative on dipstick done on unspun urine at the TOC visit
c. When applicable, clearance of signs/symptoms of urinary tract infection

f. Bacteremia of Unknown Origin: In order to be enrolled, at least one positive blood culture for the causative pathogen was required, with no identifiable primary source of infection defined at the time of study entry. In order to be found evaluable, two positive blood cultures were required and a cure was defined as a negative blood culture at both the EOT and TOC (defined as at least 3 days after therapy) visits, with the caveat that repeat cultures at the TOC visit could be omitted if the investigator believed that there were no clinical grounds upon which to justify a repeat culture.

Medical Officer's Comments: The medical officer used the following evaluability and efficacy criteria for this category:

1. In order to be evaluable, the patient needed the following:
   a. Two blood cultures, drawn from separate locations (via catheter NOT accepted) at separate times, with PURE growth of VREF.
   b. No source of infection found on an adequately performed search for such a focus.
2. In order to be considered a "cure", the patient needed the following:
   a. Negative blood cultures (a set of two) from a peripheral site for two days in a row.
   b. Negative blood culture obtained at a follow-up visit (at least 5 days post-tx), with NO positive cultures in the time period between EOT and TOC.
   c. No focus of infection developed during therapy or noted after therapy that could be seen as due to "seeding" of VREF.

g. Bone and Joint Infections: Specific evaluability criteria were not provided by the applicant in the study protocols.

Medical Officer's Comments: The evaluability and efficacy criteria used by the medical officer for this infection site were:

1. In order to be evaluable, the patient needed the following:
    a. Growth of VREF on a surgically obtained specimen of a documented bone or joint infection (documented as per clinical exam AND radiological studies)
    b. OR, two positive blood cultures (from different sites) with pure growth of VREF and a documented bone or joint infection (as per above)
2. In order to be considered a "cure", the patient needed the following:
    a. Clearance of infection clinically and either a negative repeat culture (from actual infection site) or no source available to culture
    b. After the initial debridement, no further surgical intervention was done. In cases where multiple debridements were considered "standard of care", then accepted. Otherwise, patients seen as failures.
    c. In situations where there was a prosthesis infection (such as with an artificial hip), the goal of therapy appeared to be to prevent removal of the prosthesis. Thus, removal of the prosthesis (though considered to be "standard of care" in many situations) was seen as a failure of study drug.

The last efficacy criterion is controversial, with the "standard of care" being removal of infected hardware. However, this criterion was used since the reason for enrollment of multiple patients in this category was to save the prosthetic device. The number of patients found to be a failure due to this criterion was low, being one each in Study 301 and Study 398.

h. Deep Wound Other Than Abdominal: Specific evaluability criteria were not provided by the applicant in the study protocols.

Medical Officer's Comments: The evaluability and efficacy criteria used by the medical officer for this infection site were:

1. In order to be evaluable, the patient needed the following:
    a. Deep wound infection, such as an abscess, muscle infection, parenchymal infection, etc. documented clinically and radiologically (such as on a CT scan)
    b. Cultures obtained during surgery with either pure growth of VREF or mixed infection in clinical settings where polymicrobial infection would be anticipated.
    c. Adequate surgical debridement/drainage of the infected site.
2. In order to be considered a cure, the patient needed the following:
    a. Clinical improvement and either repeat surgically obtained cultures being negative for VREF growth or no infection site available for re-culture.
    b. No further debridement or drainage needed, except in cases where this was considered to be standard of care.

i. Intravascular Site Infection: Specific evaluability criteria were not provided by the applicant in the study protocols.

Medical Officer's Comments: The evaluability and efficacy criteria used by the medical officer for this infection site were:

1. In order to be evaluable, the patient needed the following:
    a. Clinically documented infection of either a vascular structure/bed or of an intravascular device with either signs/symptoms of phlebitis or of a tunnel/site infection if a device was involved
    b. Two positive cultures with pure growth of VREF
    c. No documentation of either endocarditis or of a central catheter-related bacteremia

    NOTE: In the emergency IND studies (namely 399 and 398B), patients with concomitant infections such as endocarditis along with intravascular site infection were accepted.
2. In order to be considered a cure, the patient needed the following:
    a. Clearance of infection, clinically, and negative repeat cultures at the follow-up visit.
    b. No removal of intravascular device. Note, the goal of therapy in these patients was to be able to retain the device. Thus, removal was seen as a treatment failure, though removal is the "standard of care" in most situations.

j. Other Category: The applicant, for patients that did not clearly match any of the other infection types, used this category. It was used for either infection types seen infrequently or for situations where one of the infection types already listed was present, but where documentation or improper bacteriologic collection was an issue. Many of these patients were enrolled for primarily a clinical evaluation. Because of this, the medical officer found most unevaluable. However, as will be seen, there were several meningitis patients enrolled under this category, and the evaluability criteria used for these patients are those used in the traditional evaluation of meningitis patients.

k. Respiratory Tract Infections: Specific evaluability criteria were not provided by the applicant in the study protocols.

Medical Officer's Comments: The evaluability and efficacy criteria used by the medical officer for this infection site were:

1. In order to be evaluable, the patient needed the following:
    a. Clinical signs/symptoms consistent with a lower respiratory tract infection
    b. Radiological evidence of a new pulmonary infiltrate
    c. Sputum or BAL sample with >25 WBCs and <10 epithelial cells per HPF, and with growth of VREF. In situations where the patient was neutropenic, the WBC criterion was waived.
    d. In situations where respiratory samples were not obtained or did not grow out a pathogen, then it was acceptable to have two positive blood cultures with VREF growth and with NO apparent source of infection (other then the lower respiratory tract).
2. In order to be considered a cure, the patient needed the following:
    a. Improvement clinically and a negative repeat culture (blood or respiratory tract sample as discussed above) at the TOC visit
    b. Either resolution or improvement radiologically at the TOC visit.

7. **Overall Evaluability and Efficacy Rates:**

a. Number of Patients Enrolled Per Study:

Study 301: 257 patients
Study 398: 210 patients
Study 399: 227 patients
Study 398B: 528 patients

b. Evaluability Rates Per Study:

	Study 301	Study 398	Study 399	Study 398B
Medical Officer	117/257 (46%)	70/210 (33%)	36/227 (16%)	75/528 (14%)
Applicant	115/257 (45%)	59/210 (28%)	0/227 (0%)	211/528 (40%)

Medical Officer's Comments: Please note that the evaluability rates listed for the applicant refer to those patients which RPR considered to be fully evaluable. There was a higher proportion of patients considered to be "clinically evaluable" by the applicant.

c. Efficacy Rates Per Study for Fully Evaluable Patients:

	Study 301	Study 398	Study 399	Study 398B
Medical Officer	65/117 (56%)	32/70 (46%)	23/36 (64%)	36/75 (48%)
Applicant	74/115 (64%)	45/59 (76%)	0/0	152/211 (72%)

Medical Officer's Comments: The efficacy rates are shown for all 4 studies. Due to reasons discussed in detail previously, data from studies 301 and 398 will be emphasized in the following sections of this review.

d. Mortality Rates Per Study:

Study 301: 49.8%
Study 398: 49.5%
Study 399: 53.8%
Study 398B: 54.0%

Medical Officer's Comments: This represents "all cause" mortality, with the denominator used per study being the number of enrolled patients. Note, that in the VREF literature, the "all cause" mortality rates range from 30-70%.

e. Number of Bacteremic Patients (all indications): # Eradicated or Presumed Eradicated /# Fully Evaluable:

Study 301: Medical Officer: 19/52 eradicated/pres. eradicated (36.5%)
Applicant: 29/49 eradicated/presumed eradicated (59.2%)
Study 398: Medical Officer: 14/43 eradicated/pres. eradicated (32.6%)
Applicant: 27/37 eradicated/presumed eradicated (73.0%)

Medical Officer's Comments: It should be clarified that although the number of evaluable patients in each of the two studies is similar in the applicant's and medical officer's analysis, the actual patients differ. Differences in the evaluability criteria used for the diagnosis of "bacteremia of unknown origin" (which accounts for the largest percentage of the bacteremic patients) were detailed previously. In addition to these differences, the evaluation of patients who died on therapy also differed between the applicant and medical officer, as explained before.

8. **Evaluability and Efficacy Rates Per Specific Sites of Infection:**

This section will deal specifically with the 11 sites of infection and will present the number of patients found evaluable, reasons why patients were found unevaluable and the efficacy rates for the evaluable patients. The 4 sites where entry was dependent on positive blood cultures, namely bacteremia of unknown origin, central catheter-related infections, endocarditis and intravascular infections, will be reviewed first. This will be followed by the largest indication, intra-abdominal infections, which also accounted for the largest number of patients with concomitant bacteremia of the non-vascular infections listed in section #6. Finally, the remaining 6 indications will be presented.

Several points of clarification are needed prior to data presentation:

1. The evaluability and efficacy rates presented will be for "fully evaluable" patients, that is, patients deemed to be both clinically and bacteriologically evaluable.
2. For the unevaluable patients, it should be noted that what will be listed is the "primary" reason why a patient was found to be unevaluable. Other reasons may have been present, but the first chronologically is the one listed.
3. The indications with bacteremia (the four vascular infections plus intra-abdominal, where a large proportion of patients had concomitant bacteremia) have been looked at in particular because this is the only clearly defined and agreed upon clinical setting where VREF must be treated.
4. A large number of patients enrolled into the intra-vascular infection categories (especially bacteremia of unknown origin) and into the intra-abdominal infection category, died while on therapy. In the applicant's analysis (which was based primarily on the responses listed by the individual investigators), such patients were usually considered to be unevaluable if there was no evidence of active infection. However, there was a number of patients deemed to be "cured" by the investigator because of negative blood cultures at the time of death, this despite still being on therapy and with no follow-up off of study drug.

   This led to the dilemma of how to evaluate these patients. In the more traditional sites of infection there is commonly a clinical response seen which correlates well with the bacteriological response. For example, a patient with a complicated skin and skin structure infection will have clinical improvement associated with the eradication of the pathogen. For patients with bacteremia of unknown origin, the correlation between clinical improvement and bacteriologic outcome is more difficult to appreciate, especially in the patient population studied. While parameters such as fever, tachycardia, tachypnea, mental status, WBC count, etc. could potentially be seen as clinical "markers" for a bacteremic state, these tend to be non-specific. In the patient population studied, there commonly were multiple other medical difficulties, any one of which could possibly affect the parameters noted above. Thus, the eradication of VREF from the bloodstream can only be viewed as a potential marker or surrogate for eventual clinical improvement (which will be dependent on other factors as well).

5. Due to the problems in evaluating patients with vascular infections who died while on therapy, it was decided to analyze their last blood cultures prior to death (albeit, while still on therapy), to see if the VREF had cleared.
6. Information on patients in the intra-abdominal category who died will also be presented due to the large proportion with concomitant bacteremia. The approach taken will be somewhat different. The majority of patients in this category were post-op when enrolled, so mortality secondary to surgery needed to be accounted for. Thus, all patients who died within the first three days of therapy are categorized together. For the remaining patients, the results of either intra-abdominal cultures OR blood cultures (which were more commonly done due to their ease) will be presented.
7. In the "Reasons Why Unevaluable" tables that will be seen with each infection site, the reasons listed are as per the medical officer. There are points of clarification regarding several of the reasons, and these are listed as "Notes" under the table in the "bacteremia of unknown origin" section. These "Notes" apply to all other infection sites as well.

a. Bacteremia of Unknown Origin:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	71	62
M.O. Evaluable	17 (24%)	16 (26%)
RPR Evaluable	16 (23%)	14 (23%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	30	17
2. One + Cx Only Pre-Therapy	9	10
3. No + Cx Pre-Therapy	5	6
4. Lack of data/info	5	5
5. No follow-up visit	1	2
6. Insufficient Treatment Duration	1	0
7. Prior Enrollment	1	2
8. Prohibited Abx	0	4
9. AE leading to discontinuation	0	2
10. Other	2	0
TOTAL	54	48

Note #1: Reasons #5, 6, and 9 DO NOT include patients who died on therapy. These categories are for those patients that lived.

Note #2: In Study 398, prior enrolled patients were NOT included in the ITT population. Thus, 46 unevaluable patients listed in the table above, but 48 in the listings.

Note #3: These are the primary reasons why a patient was found unevaluable. A patient could have had several.

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	9/17 (53%)	3/16 (19%)
Total Cured/Eval RPR	7/16 (44%)	10/14 (71%)

NOTE: In Study 398, the patients found evaluable by the medical officer were not the same as those found to be evaluable by the applicant.

Status of Blood Cultures At the Time of Death:
In Study 301, 35 of the 54 unevaluable patients died while on therapy or immediately after treatment completion, while for Study 398, this applies to 25 of the 48 unevaluable patients. The following table summarizes the blood culture results prior to death (while still on therapy).

	Study 301	Study 398
1. Last two or more blood cultures negative for growth of VREF	23	12
2. Only one negative blood culture (had to be last) prior to death	7	1
3. No repeat blood cultures done (after entry cx) prior to death	2	9
4. Positive culture at time of death	3	3

NOTE: Patients in category #4 were not called a failure due to other evaluability criteria violations, such as less than 3 days of therapy.

b. Central Catheter-Related Infections:
Evaluability Rates:

	Study 301	Study 398
Total Enrolled	22	20
M.O. Evaluable	9 (41%)	6 (30%)
RPR Evaluable	9 (41%)	5 (25%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	4	1
2. No + cx Pre-therapy	6	4
3. Lack of data/info	1	3
4. Lack of f/up visit	1	2
5. Prohibited antibiotic	0	1

6. Incorrect Diagnosis	0	2
7. Insuff Tx Duration	1	0
8. AE leading to D/C	0	1
TOTAL	13	14

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	5/9 (56%)	4/6 (67%)
Total Cured/Eval RPR	7/9 (78%)	5/5 (100%)

Status of Blood Cultures at the Time of Death:

In Study 301, 7 of the 13 unevaluable patients died while on therapy or immediately after treatment completion, while for Study 398, this applies to 2 of the 14 unevaluable patients. The following table summarizes the blood culture results prior to death (while still on therapy).

	Study 301	Study 398
1. Last two or more blood cultures negative for growth of VREF	6	2
2. Only one negative blood culture (had to be last) prior to death	1	0

c. Endocarditis:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	3	14
M.O. Evaluable	1 (33%)	4 (29%)
RPR Evaluable	1 (33%)	4 (29%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	1	2
2. No + cx Pre-therapy	0	2
3. Lack of data/info	0	1
4. Prohibited Antibiotic	0	3
5. Prior Enrollment	1	1
6. Insuff Tx Duration	0	1
TOTAL	2	10

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	0/1 (0%)	1/4 (25%)
Total Cured/Eval RPR	0/1 (0%)	2/4 (50%)

Status of Blood Cultures at the Time of Death:

In Study 301, 2 of the 2 unevaluable patients died while on therapy or immediately after treatment completion, while for Study 398, this applies to 4 of the 10 unevaluable patients. The following table summarizes the blood culture results prior to death (while still on therapy).

	Study 301	Study 398
1. Last two or more blood cultures negative for growth of VREF	0	4
2. Only one negative blood culture (had to be last) prior to death	1	0
3. No repeat blood cultures done (after entry cx) prior to death	0	0
4. Positive culture at time of death	1	0

NOTE: Patients in category #4 were not called a failure due to other evaluability criteria violations, such as less than 3 days of therapy.

d. Intravascular Infections: This category was not utilized in Study 398. Both the medical officer and applicant enrolled three patients with infected phlebitis due to VREF into Study 301, with all 3 found to be evaluable. The medical officer called all 3 cases failures, while the applicant called 2 out of 3 a failure.

e. Intra-Abdominal Infections:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	89	59
M.O. Evaluable	46 (52%)	21 (36%)
RPR Evaluable	43 (48%)	17 (29%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	21	19
2. No + cx Pre-therapy	3	0
3. Lack of data/info	6	3
4. No f/up visit	0	6
5. Insufficient Tx Duration	0	1
6. Prior Enrollment	4	1
7. Prohibited Antibiotic	2	3
8. AE leading to D/C	0	1
9. Incorrect Diagnosis	0	2
10. Inadequate Drainage	7	3
TOTAL	43	39

NOTE: In Study 398, one prior enrolled patient was not included in the ITT population. Thus, 38 unevaluable patients listed in the table above, but 39 in the listings.

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	23/46 (50%)	8/21 (38%)
Total Cured/Eval RPR	24/43 (56%)	13/17 (76%)

NOTE: In Study 398, the patients found evaluable by the medical officer were NOT the same as those found to be evaluable by the applicant. Thus, the efficacy rates differ not due to different interpretation of the same patients, but due to different patients altogether.

Culture Results At the Time of Death:

In Study 301, 28 of the unevaluable patients died while on therapy or immediately after treatment completion, while for Study 398, this applies to 20 of the unevaluable patients. The following table summarizes the blood and/or intra-abdominal culture results prior to death (while still on therapy).

	Study 301	Study 398
1. Died Within 3 days of Therapy Start	3	7
2. Died After 3rd Day of Therapy:		
a. Last two or more blood cultures negative for growth of VREF	9	4
b. Only one negative blood culture (had to be last) prior to death	3	4
c. No repeat blood cultures done (after entry cx) prior to death	3	1
d. Positive culture at time of death	10	4

NOTE: Patients in category "d" were not called a failure due to other evaluability criteria violations, such as lack of appropriate surgical therapy.

f. Bone and Joint Infections:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	8	20
M.O. Evaluable	5 (63%)	8 (40%)
RPR Evaluable	4 (50%)	5 (25%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	1	4
2. No + cx Pre-therapy	0	1
3. Lack of data/info	0	2
4. Lack of f/up visit	1	2
5. Prohibited antibiotic	0	3
6. Other	1	0
TOTAL	3	12

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	2/5 (40%)	6/8 (75%)
Total Cured/Eval RPR	3/4 (75%)	5/5 (100%)

g. Deep Wound Other Than Abdominal: This category was used in Study 301 (not in Study 398) and essentially included patients with deep wound infections involving muscles or parenchyma. Four patients were enrolled into this category, with the medical officer finding all 4 evaluable and cured. The sponsor found 3 of the 4 evaluable, with all 3 cured.

h. Other:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	10	8
M.O. Evaluable	3 (30%)	4 (50%)
RPR Evaluable	4 (40%)	4 (50%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	3	2
2. No + cx Pre-therapy	1	1
3. Lack of data	1	0
4. Lack of f/up	1	1
5. Proh Abx	1	0
6. Prior Enrollment	0	1
TOTAL	7	5

NOTE: In Study 398, one prior enrolled patient was not included in the ITT population. Thus, 4 unevaluable patients listed in the table above, but 5 in the listings.

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	3/3 (100%)	2/4 (50%)
Total Cured/Eval RPR	4/4 (100%)	2/4 (50%)

The three patients found evaluable (by M.O.) and cured in Study 301 had the following infections:

1. Patient with an infection at a lung biopsy site.
2. Patient with ascites of unclear etiology.
3. Patient s/p radical GU and GI surgery, with multiple sites of VREF infection.

The four patients found evaluable by the medical officer in Study 398 had the following infections:

1. Two patients with VREF meningitis. One deemed a cure and one a failure.
2. One patient with a A-V graft infection who was cured.
3. One patient with an infected left ventricular assistance device infection. Failed therapy.

i. Respiratory Tract Infections:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	5	5
M.O. Evaluable	2 (40%)	1 (20%)
RPR Evaluable	1 (20%)	1 (20%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	2	1
2. No + cx Pre-therapy	1	2
3. Lack of data	0	1

4. Prior Enrollment	0	1
TOTAL	3	5

NOTE: In Study 398, one prior enrolled patient was not included in the ITT population. Thus, 4 unevaluable patients listed in the table above, but 5 in the listings.

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	1/2 (50%)	0/1 (0%)
Total Cured/Eval RPR	1/1 (100%)	0/1 (0%)

j. Skin and Skin Structure Infections:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	25	16
M.O. Evaluable	10 (40%)	5 (31%)
RPR Evaluable	15 (60%)	5 (31%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	4	4
2. No + cx Pre-therapy	2	2
3. Lack of data	4	2
4. Lack of f/up	1	0
5. Prohibited Antibiotic	1	0
6. Prior Enrollment	3	0
7. Incorrect Diagnosis	0	2
8. AE Leading to D/C	0	1
TOTAL	15	11

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	7/10 (70%)	3/5 (60%)
Total Cured/Eval RPR	11/15 (73%)	4/5 (80%)

k. Urinary Tract Infections:

Evaluability Rates:

	Study 301	Study 398
Total Enrolled	26	12
M.O. Evaluable	17 (65%)	6 (50%)
RPR Evaluable	16 (62%)	4 (33%)

Primary Reasons For Classification as Unevaluable:

	Study 301	Study 398
1. Died During Therapy	4	2
2. No + cx Pre-therapy	2	2
3. Lack of data	1	1
4. Lack of f/up	2	0
5. Incorrect Diagnosis	0	1
TOTAL	9	6

Efficacy Rates:

	Study 301	Study 398
Total Cured/Eval M.O.	11/17 (65%)	6/6 (100%)
Total Cured/Eval RPR	13/16 (81%)	4/4 (100%)

9. **Specific Pathogens**:

Except for Study 301, patients with pathogens other than VREF could be enrolled. Overall, approximately 10% of both the ITT and fully evaluable patients were enrolled with a pathogen other than VREF, with methicillin-resistant *Staphylococcus aureus* (MRSA) accounting for the majority of these.

In regard to MRSA, the table below lists the total number of patients per study who were enrolled with MRSA as the entry pathogen, the number found fully evaluable by the medical officer, and the overall cure rate for the evaluable cohort. The applicant found 20 patients with MRSA as the entry pathogen to be fully evaluable.

	Number Reported	Number Evaluable	Cured/Evaluable
Study 301	0	0	0
Study 398	25	9	5/9 (56%)
Study 398B	40	2	1/ 2 (50%)
Study 399	12	3	3/3 (100%)
TOTAL	77	14	9/14 (64%)

Medical Officer's Comments Concerning MRSA: Overall, the cure rates seen (which represent bacterial eradication or presumed eradication and clinical improvement or cure) are promising if one considers the severity of illness seen in the patient population enrolled into the Emergency Use studies. However, several comments need to be made:

1. *Number of Unevaluable Patients: Only 18% of the patients were found evaluable, with a "lack of data" (such as missing data from EOT and TOC visits) being the primary reason why patients in this group were found to be unevaluable. Given the large number of unevaluable patients, it is uncertain how reliable the estimate of the response rates is based on the evaluable patient population.*
2. *Site of Infection: Of the 14 patients, 10 entered the study with a diagnosis of bone and joint infection, with one patient each in the following 4 diagnoses: bacteremia of unknown origin, central catheter-related infections, endocarditis, and skin and skin structure infections. Of the patients with a bone and joint infection, 7 (70%) were cured. Overall, these patients were more clinically stable than most patients enrolled in these Emergency use studies, with the bone and joint infection commonly being the sole medical problem.*

10. **Adverse Events:**

Please see the safety review by Mr. David Bostwick and Dr. Susan Thompson for full details.

11. **Other Issues:**

a. Development of Resistance: In Study 301, on-therapy and/or post-therapy stool surveillance cultures were done almost routinely, though not specified in the study protocol. This was not the case in the other 3 studies. For a large percentage of patients, the stool surveillance cultures were done exclusively to see if VREF was still present as a colonizer, and susceptibility testing to Synercid was not routinely performed. However, of the patients who did have susceptibility testing performed, 12 patients (patient numbers: 0104, 0408, 0410, 0506, 1702, 2301, 2309, 2331, 3109, 3204, 3401, and 3505) had a VREF strain isolated from the during or post-therapy stool culture with an MIC to Synercid 4x or greater than that of the initial isolate.

In addition, in Study 301 (which enrolled 257 patients), seven patients had the emergence of resistance to Synercid on therapy (i.e., cultures positive for VREF from the same site of infection pre-therapy and at the end of therapy showed at least 4-fold increase in MIC to Synercid.) The sites of infection affected were:

Blood Cultures Showing Resistant Strain:

- Pt. 2302: Entry blood culture with VREF strain with a MIC of 1.0 mcg/mL; increased to [redacted] on a blood culture done on the day of death.

- Pt. 2311: Entry blood culture VREF strain with a MIC of 0.5; increased to [redacted] on day of therapy #18.
- Pt. 3002: Entry blood culture VREF strain with a MIC of 1.0; increased to [redacted] on day of therapy #18.
- Pt. 3402: Entry blood culture VREF strain with a MIC of 1.0; increased to [redacted] on the day of death.

Intra-Abdominal (IA) Cultures Showing Resistant Strain:

- Pt. 1103: Entry IA culture VREF strain with a MIC of 1.0; IA culture on the day of death showed increase in MIC to [redacted]
- Pt. 2318: Entry IA culture VREF strain with a MIC of 0.5; IA culture on the day of death showed increase in MIC to [redacted]

Others:

- Pt. 0208: Entry urine culture VREF strain with a MIC of 1.0 mcg/mL; positive urine culture on the last day of therapy with MIC increased to [redacted]

In Study 398, there were three patients (of 210 who received study drug) who had an on or post-therapy culture VREF strain that had a MIC of 4x or greater than that of the entry culture strain. All 3 cases involved intra-abdominal cultures.

b. *Enterococcus faecalis* Overgrowth: A fairly common phenomenon seen in each of the 4 studies (but most in Study 301, where surveillance stool cultures were done in the majority of patients) was the growth on stool cultures of *E. faecalis* several days after the initiation of Synercid. This could be seen as an expected phenomenon considering the poor activity of Synercid against this organism. Please refer to the safety summary by Mr. David Bostwick and Dr. Susan Thompson regarding clinical infections due to *Enterococcus faecalis*.

12. **Discussion**:

a. Adequacy of Studies: The 4 Emergency-Use/VREF studies do not provide clear evidence for efficacy when analyzed by site of infection, either for mortality or resolution of infections. The reasons for this are as follows:

1. Lack of Concurrent Control: When initially designed, with input from the Division of Anti-Infective Drug Products (during Subpart E discussions concerning development of Study 301), it was realized that it would be unethical to conduct a placebo-controlled study, yet also problematic to conduct a comparative trial because the selection of a single drug or drug combination would be difficult. However, it was agreed that the overall results of these emergency use/VREF studies would be adequate to garner an approval for the treatment of VREF infections if one of two criteria were satisfied:

    a. There was a dramatic improvement in overall mortality as compared to a historical perspective for this disease state.

b. The results were comparable, both overall and for specific sites of infection, to those seen in the literature. That is, an adequate historical control would be defined and the results compared to it.

If neither of these two criteria is met, then the lack of a concurrent control in these studies becomes more critical.

2. Historical Control: A review of the VREF literature is provided by the applicant in their Integrated Summary of Efficacy section of the NDA submission. This review is informative and well structured, however it brings to light difficulties with the attempt to establish an adequate historical control. Several of the major problems are:
    a. The studies have varying regimens used to treat VREF infections with both different drug combinations used and different dosing schedules for the actual agents chosen.
    b. The infections studied differ from those seen in the Synercid trials, with the majority of the studies in the literature dealing with "bacteremic" patients, though not necessarily of unknown origin. In addition, the definition of "bacteremic" differs from that used in the Synercid studies.
    c. Endpoint assessment differed from those used in these trials, with the studies in the literature primarily analyzing patients at an end-of-therapy visit. Additionally, a percentage of studies do not analyze the "all-cause" mortality rates.
    d. The small numbers of patients enrolled per study.

Therefore, in light of the above, it is difficult to establish an adequate historical control with which to compare the results of the Synercid trials.

3. Need for Therapy: The VREF literature does bring to light the controversy about whether to treat VREF infections at certain sites. For example, in clinical situations where multiple pathogens are present (such as would be seen in complicated skin and skin structure infections and intra-abdominal infections) it appears that the adequate therapy of the concomitant non-VREF pathogens will lead to adequate clinical outcomes despite the lack of therapy for the VREF component of the infection.
4. Results: The low overall response rates observed in these studies and the low evaluability rates, lead to uncertainty about whether the studies submitted provide substantial evidence of the effectiveness of Synercid for the treatment of infections due to VREF.

b. Clearance of Bacteremia: The studies, especially Study 301 and 398A, provide evidence that treatment with Synercid is associated with clearance of bacteremia. Clearance was established in the evaluable patients by negative blood cultures done

off of therapy. However, in the unevaluable patients who died on therapy but with negative blood cultures, there is the "apparent" clearance of the organism.

1. Clearance of bacteremia cannot be viewed as a clinical benefit in and of itself. There are two scenarios in which patients with bacteremia were found. In the first, a focus of infection was identified and the bacteremia occurred as an extension of this infection (such as seen with intra-abdominal infections or complicated skin and skin structure). In this situation, the clearance of the actual site of infection would lead to the clearance of the bacteremia as well. The clinical benefit of the use of Synercid could be assessed by evaluating the response at the actual site of infection. In the second setting, bacteremia is of unknown origin, with no focus found. In this setting, clinical improvement would be more difficult to establish due to the lack of an objective evaluation of an actual site of infection. Thus, in both situations, the clearance of bacteremia, while important, cannot be seen as indicative of ultimate clinical improvement or cure.
2. The VREF literature is clear that VREF bacteremia (be it of unknown origin or associated with a focus) should be treated and that clearance of VREF from the bloodstream can be seen as beneficial to the patient. In fact, while there is debate about whether to treat VREF at various sites of infection, there is consensus that bacteremia should be treated.
3. Thus, while clearance of bacteremia is not a clinical benefit by itself, it can be seen as likely to predict clinical benefit.

Thus, it is proposed that the clearance of VREF bacteremia be viewed as a surrogate endpoint likely to predict clinical resolution of infection.

13. **Conclusions:**

a. Given that infections with VREF, especially when associated with a bacteremic state, are a serious and life-threatening condition, and that no approved alternative is available, Synercid may be viewed as representing a needed therapeutic option for the treatment of VREF infections.
b. In light of the problems discussed above, the approval of Synercid could be based upon its effect on a surrogate endpoint, namely, the clearance of VREF bacteremia.
c. Thus, it is recommended that Synercid be approved under Subpart H regulations, and confirmatory clinical studies be designed and ongoing at the time of approval.
d. In regard to the confirmatory clinical studies, the following aspects should be included:
    1. The studies should be comparative.
    2. Patients with infections where bacteremia is most common should be the patient population enrolled in the studies.
    3. Evaluability endpoints should be consistent with IDSA/FDA guidelines and should be discussed with the division prior to study initiation.
    4. All-cause mortality should be analyzed as a secondary endpoint.

e. Other phase 4 commitments are the following:

1. Pediatric data: pharmacokinetic studies and review of the safety and efficacy of Synercid in this population should be done.
2. Drug interaction studies, involving drugs metabolized by the CYP 3A4 enzyme.
3. Surveillance data, analyzing the development of resistance to Synercid (especially among VREF strains) and the impact of this resistance on clinical outcomes.

/S/ 7-10-98

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M.O./HFD-520

ORM-520/DivDir/GChikami /S/ 7/23/98
ORM-520/ClinTeamLeader/KRoberts 7/16/98

[i] Maki D, Weise C, Sarafin H. A semiquantitative method for identifying intravenous catheter-related infections. *N Engl J Med* 1997;296:1305-1309.

[ii] Blumberg EA, Robbins N, Adimora A, et al. Persistent fever in association with infective endocarditis. *Clin Infect Dis* 1992;15:983-990.

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CONCLUSIONS REGARDING PROPOSED CLINICAL INDICATIONS

The following is a summary of the final conclusions and labeling for the various indications sought by the Applicant. For full details please see the appropriate medical officer review.

[redacted]

3. **Complicated Skin and Skin Structure Infections:** The conclusion of the reviewing medical officer (Dr. Thompson) was that Synercid should not be recommended for approval for this indication. The clinical team leader (Dr. Roberts) has recommended approval. (Refer to team leader's memo.) Dr. Chikami concurred with this recommendation. Labeling for this indication is proposed to read as follows:

   "**Complicated skin and skin structure infections** including cellulitis and traumatic wound infections caused by *Staphylococcus aureus* (methicillin susceptible) or *Streptococcus pyogenes*.

4. **Infections caused by *Staphylococcus aureus*:**

   a. This pathogen is found at a prevalence sufficient to allow it to be studied at a particular infection site in a controlled clinical trial. In addition, this pathogen would be labeled not as a separate pathogen-driven indication but as a pathogen listed under a traditional indication.

   b. In regard to the data obtained from the non-comparative studies, there are approved comparator agents for both [redacted] susceptible and [redacted] resistant strains of *Staphylococcus aureus*. Therefore, a comparative study would be expected and data from non-comparative studies could be seen only as supportive.

   c. The data to support inclusion of *Staphylococcus aureus* [redacted] susceptible or [redacted] resistant) under the specific indications studied are discussed in the reviews of the clinical trials for each specific infection.

/S/ 8/21/98

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Medical Officer/ORM-520

ORM-520/DivDir/GChikami. /S/ 8/24/98
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8/21/98

HFD-530 Dillon (DAY 1)

INTRODUCTORY COMMENTS

AUG 24 1998

1. General Comments:

This is a brief overview of the indications sought by the Applicant, the studies submitted in support of these indications, and a summary of the phase 2 studies done. Full details regarding this new molecular entity and the regulatory history of its development can be found in the reviews of the various disciplines as well as the individual phase 3 study reviews.

The Applicant submitted two NDA's on September 5th, 1997 for review, NDA 50-747 and NDA 50-748. NDA 50- 747 was a priority review in which the Applicant sought approval of the use of Synercid for the treatment of infections due to vancomycin-resistant *Enterococcus faecium* (VREF). An Approvable action was taken on this NDA on March 5, 1998. NDA 50-748 is a standard review. Pre-clinical information was submitted under NDA 50-748 and was cross-referenced for use in support of NDA 50-747. What follows is the proposed indications sought by the Applicant and includes indications from both NDA's.

2. Indications Sought:

"Synercid is indicated in adults for the treatment of the following infections when caused by susceptible strains of the designated microorganisms, for which intravenous therapy is appropriate.

"Synercid should be used in combination with appropriate anti-Gram-negative antibiotics if culture-proven or suspected pathogens are Gram-negative.

"Complicated skin and skin structure infections caused by *Staphylococcus aureus* (including resistant strains), *Staphylococcus epidermidis* *Streptococcus agalactiae*, and *Streptococcus pyogenes*, including cases associated with concurrent bacteremia with these microorganisms.

"Infections due to Vancomycin-resistant *Enterococcus faecium* (VREF), including cases associated with concurrent bacteremia.

"Infections caused by *Staphylococcus aureus* (including susceptible and resistant strains), in patients failing other therapy, including cases associated with concurrent bacteremia.

"Synercid was used successfully in a limited number of pediatric patients in non-comparative clinical studies.

"Synercid can be used for treatment of the above indications in beta-lactam-, quinolone- or glycopeptide-allergic or –intolerant patients."

3. Studies Submitted:

a. VREF Infections Indication: Four non-comparative studies were submitted (Studies 301, 398, 398B, and 399) and reviewed by Dr. Rakowsky.

b. Complicated Skin and Skin Structure Infections Indication: Two comparative studies were submitted (Studies 304 and 305) and reviewed by Dr. Thompson.

e. Infections Caused by *Staphylococcus aureus* Indication: No specific studies done. Applicant referred to the experience in treating infections due to this pathogen in the non-comparative VREF studies (which also enrolled patients with non-VREF Gram-positive pathogens) and in the comparative studies for the skin and skin structure [redacted]

4. **Phase 2 Studies:**

In addition to the studies listed above, the Applicant also submitted study reports from four phase 2 studies. A brief summary of each study follows. Note, all conclusions are as per the Applicant.

4.a. Study 201: This study was initiated to determine an effective dose of Synercid in patients with [redacted] Patients were selected based upon clinical, radiological, and microbiological criteria. Fifteen patients were enrolled and randomized to receive doses of Synercid ranging from 3 to 9 mg/kg every 12 hours. Ten of the 15 patients were found to be fully evaluable by the Applicant, with 8 of these 10 patients seen as overall therapeutic successes. Five patients presented with concomitant bacteremia, 3 patients in the 3 mg/kg dosing arm and 2 in the 6 mg/kg dosing arm. One of the patients in the 3 mg/kg arm did not have clearance of bacteremia, while the other 4 patients had successful eradication.

In regard to adverse events (AE), no dose-effect relationship could be established for adverse clinical, venous or laboratory events. Six patients reported non-venous adverse events, with one discontinuation due to a serious AE. Thirteen patients had venous adverse events, with two discontinuations. Abnormal laboratory values, particularly elevations in liver enzymes (AST/ALT), occurred in 9 patients, with one discontinuation.

The conclusion of the study was that the 3 mg/kg dosing regimen was not effective, with a 6 mg/kg every 12 hour dosing regimen being the minimum that should be considered for future clinical trials.

4.b. Study 202: This study was initiated to determine an effective dose of Synercid in patients with erysipelas. Nine patients were enrolled and randomized to receive doses of Synercid ranging from 3 to 9 mg/kg every 12 hours. Eight patients were found to be fully evaluable, with 6 out of these 8 seen as clinical cures. Both failures occurred in the 3 mg/kg arm.

In regard to AEs, no dose-effect relationship could be established for adverse clinical, venous or laboratory events. All patients experienced a venous adverse event. The most common non-venous adverse events were gastrointestinal in nature and rated usually of mild to moderate intensity. One patient was discontinued due to a severe gastrointestinal AE. No remarkable laboratory abnormalities were reported during the study.

The conclusion of the study was that the 3 mg/kg dosing regimen was not effective, and that a minimum of 4.5 mg/kg every 12 hours would be needed for adequate coverage of erysipelas.

4.c. Study 203: This double-blind, randomized, multicenter, comparative, dose-ranging clinical study was conducted to evaluate and compare the safety and efficacy of two different doses of Synercid (5.0 mg/kg and 7.5 mg/kg every 12 hours) compared with that of ceftriaxone (1 gram once daily) when administered for 5 to 14 days to patients [redacted] The number of patients enrolled in each arm was: 48 patients in the 5 mg/kg group, 45 patients in the 7.5 mg/kg group, and 54 patients in the ceftriaxone group. The percentage of patients found clinically evaluable was approximately 65% and the clinical success rates for this subgroup of patients were: 74.2% for the 5 mg/kg arm, 75.0% for the 10 mg/kg arm, and 80.5% for the ceftriaxone arm. Due to the low number of evaluable patients, lower than anticipated success rates (the power of the study was partially based upon an anticipated success rate of 90%), and imbalances in the demographic/past medical history profiles of the patients enrolled in each arm, no robust conclusions could be drawn from this study regarding dosing regimen. However, an intent-to-treat analysis showed a clinical success rate of only 36.4% in the 5 mg/kg arm, which suggested that this dosing regimen may be inadequate for the treatment of [redacted] in more severely ill patients.

The incidence of adverse non-venous AEs was comparable among the three treatment groups, while venous AEs were higher in the two Synercid arms. Additionally, the 7.5 mg/kg group had a higher incidence of venous AEs, suggesting that venous tolerability may be related to concentration of Synercid in the infusion fluid. Results of laboratory evaluations were comparable between treatment groups, with the exception of increases in conjugated bilirubin which were more frequent in the Synercid groups. However, elevations of liver enzymes were comparable between all three treatment groups.

4.d. Study 204: This was an evaluator-blinded, randomized, multicenter, comparative, dose-ranging study conducted to evaluate the safety and efficacy of two different doses of Synercid (5.0 mg/kg and 7.5 mg/kg every 8 hours) compared with that of vancomycin (1 gram every 12 hours) when administered for 5 to 14 days to patients with central catheter-related Gram-positive bacteremia. Thirty-nine patients were enrolled, with only 23 of these patients found to have a confirmed central catheter-related Gram-positive bacteremia at baseline. Additional problems which occurred during the study included poor follow-up (with only 8 patients returning at the late follow-up period), absence of randomization (which occurred due to slow patient enrollment) and unblinding of nearly all evaluators during the study. Due to these problems robust conclusions could not be reached (with less than 5 fully evaluable patients in each arm), though results suggested that the Synercid regimens were comparable or more efficacious than vancomycin.

The incidence of adverse non-venous clinical events was slightly higher in the Synercid 7.5 mg/kg arm, although for drug-related events the three groups had comparable rates. Overall, around 25% of patients reported a venous adverse event, with rates comparable between study arms. Four patients died during the study (one each in the vancomycin and Synercid 5.0 mg/kg arms, and two patients in the Synercid 7.5 mg/kg arm) but none of these deaths were seen as drug-related by the investigators. Finally, results of laboratory evaluations were comparable between treatment groups.

/S/ 8-21-98

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CLINICAL REVIEW OF EMERGENCY USE SAFETY INFORMATION
NDA 50-747

Date of Submission: The original NDA was submitted on September 5, 1997, and it contained safety data through January 8, 1996. The safety update report was submitted on January 5, 1998, and it contains safety data through October 31, 1997.

Date of Review Initiation: March 2, 1998

Date Review to Supervisor: April 10, 1998

Drug: Synercid (quinupristin/dalfopristin) IV

Applicant: Rhône-Poulenc Rorer Pharmaceuticals, Inc.
Collegeville, PA 19426

Proposed Indications: Approval for Synercid is requested for the following indications: complicated skin and skin structure infections; [redacted] infections due to Vancomycin-resistant *Enterococcus faecium*; and infections caused by *Staphylococcus aureus* (including MRSA and MSSA).

Proposed Dosage and Administration: The recommended dose is 7.5 mg/kg. The recommended treatment duration for VREF (the indication supported by the emergency use studies) depends on the site and severity of infection.

Material Reviewed: This safety review concerns the emergency use studies only, since these studies are the principal support for the VREF indication. This indication is to be acted upon first. The other indications listed above and submitted to NDA 50-748 will be acted upon at a later date. A separate clinical review will be written for the safety data supporting them.

Background: The following table presents the number of patients exposed to Synercid in various emergency-use studies. This tabulation includes information from the January 5, 1998 safety update. Nearly all patients received 7.5 mg/kg doses of Synercid, with 227 patients dosed q 12 h and the remainder dosed q 8 h. Complete and consistent gathering of safety data took place only in study 301.

Study Number	Countries	Number of patients
301	U.S.	263
397	U.S.	120
398A	U.S.-Europe	219
398B	U.S.-Europe	528
398C	Global	1071 in U.S.
399	U.S.-Europe	227
Total		2,428

The data from studies 397 and 398C are available only in summary from the safety update. No judgment has been made in the safety update concerning the possible relationship of the reported reaction to drug use, except for serious adverse events.

This review will address the following topics:

I. Clinical Adverse Events in VREF Studies
II. Laboratory Adverse Events in VREF Studies
III. Comments on Arrhythmias and Drug-Drug Interactions
IV. Conclusions

Review:

I. Clinical Adverse Events in VREF Studies

A. Safety update (January 9, 1996 through October 31, 1997)

There were a total of 512 reactions in the 1,231 patients in the safety update (41.6%). The most frequent reports were of "aggravation reaction" (not defined), 119 (9.7%); heart arrest, 59 (4.8%); apnea, 58 (4.7%); hypotension, 56 (4.5%); acute myeloblastic leukemia 33 (2.7%); gastrointestinal hemorrhage and kidney failure, 27 each (2.2%); dyspnea, 25 (2.0%); and "infection" [redacted] 23 each (1.9%).

The following serious adverse events were assessed as being possibly or probably related to Synercid administration (some patients had more than one reaction): myalgia 3 (0.2%); vomiting, hemorrhage 2 each (0.2%) and single reports of arthralgia, hyponatremia, nausea, anemia, "infection", phlebitis, asthenia, pain, abnormal liver function tests, injection site inflammation, duodenal ulcer hemorrhage, and encephalopathy.

No reports of deaths or discontinuations were included with the safety update.

B. Study 301

This was a prospective study in VREF infections with adequate documentation of data related to both efficacy and safety. The study was conducted from October, 1994 to February, 1996.

i. Deaths: There were 128 deaths in the 263 patient study population (48.7%). Only two of the deaths were considered to be remotely related to Synercid use. One patient suffered a coagulation disorder and the other organ failure secondary to sepsis.

ii. Most common non-venous adverse events: Adverse non-venous events were reported in 261 (99.2%) of the patient population. There were 77 (29.3%) events which were considered to be probably or possibly related to Synercid therapy. The following table presents these events by body system (some patients experienced more than on event):

Body System /Adverse Event	Number (%) of Patients
Musculoskeletal system	**30 (11.4)**
Arthralgia	26 (9.9)
Myalgia	20 (7.6)
Body as a whole	**19 (7.2)**
Pain	10 (3.8)
Asthenia	6 (2.3)
Digestive system	**19 (7.2)**
Nausea	10 (3.8)
Skin & appendages	**11 (4.2)**
Rash	8 (3.0)
Cardiovascular system	**6 (2.3)**
Urogenital system	**5 (1.9)**
Metabolic & Nutritional Disorders	**5 (1.9)**
Hemic & lymphatic system	**3 (1.1)**
Respiratory system	**2 (0.8)**
Nervous system	**2 (0.8)**

It should be noted that included with the safety update was a new tabulation of musculoskeletal reactions for this study which presented a total of 79/257 = 30.7% cases of "musculoskeletal syndrome" (not defined) in study 301. There is no explanation why the total number of patients in this new presentation is 257 rather than 263, nor the origin of the 49 new reactions.

iii. Venous adverse events: There were 73 patients in this study who had the drug administered by peripheral catheter. Thirty-eight (52.1%) of these patients reported an adverse venous event (pain, edema, inflammation). Changes in infusion sites due to irritation occurred in 24/73 (32.9%) of these patients.

iv. Events leading to discontinuation: Eighty-three patients (31.3%) discontinued therapy due to adverse events. Most of these patients died, and their discontinuations (with the exception of the coagulation disorder and sepsis cases, above) were not considered related to study drug therapy. However, 16 patients experienced events possibly or probably related to study drug therapy which resulted in discontinuation

(some patients had more than one reaction). These events included: arthralgia 8 (3.0%), myalgia 7 (2.6%), nausea 3 (1.1%), myasthenia 2 (0.7%) and single reports of flatulence, pain, pharyngitis, dysphagia, dizziness, chest pain, asthenia, rash, vomiting and anorexia.

v. Serious adverse events: There were 180 adverse events (67.9%) classified as serious (other than deaths). Three of these were considered possibly or probably related to study drug treatment, including reports of ventricular tachycardia, hyperbilirubinemia, and syncope and hypotensive episodes in one patient.

C. Study 398A

This was a prospective study in primarily VREF infections, with relatively good documentation of data related to efficacy and safety. The study was conducted from May, 1995 to March, 1996.

i. Deaths: There were 104 deaths in the 219 patient study population (47.4%). Many patients had severe underlying illness and poor prognosis at study entrance. None of the deaths were considered related to Synercid, with the exception of one case of pneumonia and a separate case of sepsis; both were considered remotely related.

ii. Most common non-venous adverse events: Adverse non-venous events were reported in 147 (67.1%) of the patient population. There were 39 (17.8%) events which were considered probably or possibly related to Synercid therapy. The following table presents these events by body system (some patients experienced more than one event):

Body System /Adverse Event	Number (%) of Patients
Body as a whole	**5 (2.3)**
Cardiovascular system	**1 (0.5)**
Digestive system	**8 (3.7)**
Nausea	6 (2.7)
Hemic & lymphatic system	**2 (0.9)**
Metabolic & Nutritional Disorders	**1 (0.5)**
Musculoskeletal system	**19 (8.7)**
Arthralgia	17 (7.8)
Myalgia	9 (4.1)
Nervous system	**3 (1.4)**
Skin & appendages	**5 (2.3)**
Urogenital system	**2 (0.9)**

It should be noted that included with the safety update was a new tabulation of musculoskeletal reactions for this study which presented a total of 21/210 = 10.0% cases of "musculoskeletal syndrome" in study 398. There is no explanation why the total number of patients in this new presentation is 210 rather than 219, nor the origin of the 2 new reactions.

iii. Venous adverse events: There were only 44 patients in this study who had the drug administered by peripheral catheter. Seventeen (38.6%) of these patients reported an adverse venous event (pain, edema, inflammation).

iv. Events resulting in discontinuation: Eighty patients (36.5%) discontinued therapy due to adverse events. Most of these patients died, and their discontinuations (with the exception of the pneumonia and sepsis cases, above) were not considered related to study drug therapy. However, 15 patients experienced events possibly or probably related to study drug therapy which resulted in discontinuation (some patients had more than one reaction). These events included: arthralgia 7 (3.2%), myalgia 5 (2.3%), rash and pruritus 2 each (0.9%), and single reports of vomiting, nausea, pain, pancytopenia, acidosis, hypertonia, and infection site inflammation.

v. Serious adverse events: There were 33 adverse events (15.1%) classified as serious (other than deaths). Four of these were considered possibly or probably related to study drug treatment, including single reports of granulomatous hepatitis, pancytopenia, metabolic acidosis and hematuria.

D. Study 398B

This was a prospective study in primarily VREF infections, though other Gram positive infections were allowed. Documentation was less complete than in the 2 studies reviewed above. The study was conducted from January to December, 1996.

i. Deaths: There were 278 deaths in the 528 patient study population (52.6%). One death (heart arrest) was considered possibly related to Synercid therapy. There were 4 cases of multi-organ failure considered remotely related to Synercid therapy, as well as one case of sepsis and one case of leukemia.

ii. Most common non-venous adverse events:
Adverse non-venous events were reported in 389 (73.7%) of the patient population. There were 104 (19.7%) which were considered probably or possibly related to Synercid therapy. The following table presents these events by body system (some patients experienced more than one event):

Body System /Adverse Event	Number (%) of Patients
Body as a whole	**15 (2.8)**
Digestive system	**28 (5.3)**
Nausea	26 (4.9)
Vomiting	13 (2.5)
Musculoskeletal system	**65 (12.3)**
Arthralgia	52 (9.8)
Myalgia	44 (8.3)

It is noted that included with the safety update was a new tabulation of musculoskeletal reactions for this study which presented a total of 75/515 = 14.6% cases of "musculoskeletal syndrome" in study 398B. There is no explanation why the total number of patients in this presentation is 515 rather than 528, nor the origin of the 10 new reactions.

iii. Venous adverse events: There were 78 patients in this study who had the drug administered by peripheral catheter. Thirty-three (42.3%) of these patients reported an adverse venous event (pain, edema, inflammation).

iv. Events leading to discontinuation: Two hundred twenty-nine patients (43.3%) discontinued therapy due to adverse events. Most of these patients died, and their discontinuations (with the exceptions noted above) were not considered related to study drug therapy. However, 27 patients experienced events possibly or probably related to study drug therapy which resulted in drug discontinuation (some patients had more than one reaction). These events included: arthralgia 12 (2.3%), myalgia 10 (1.9%), nausea 6 (1.1%), vomiting 5 (0.9%), rash and anemia 4 each (0.8%), asthenia 2 (0.4%) and single reports of gastrointestinal hemorrhage, hepatitis, fever, pharyngitis, headache, diarrhea, abdominal pain, tachycardia, myasthenia and heart arrest.

v. Serious adverse events: There were 328 (62.1%) adverse events classified as serious (other than deaths). Eight of these were considered possibly or probably related to study drug treatment, including 3 cases of anemia, nausea and vomiting in one patient, one each of fever, hypotension, gastrointestinal hemorrhage, and arthralgia and myalgia in one patient.

E. Study 399

This was a retrospective collection of data from emergency IND's in which documentation was inconsistent. The study was conducted from March, 1993 to August, 1995.

i. Deaths: There were 106 deaths in the 227 patient study population (46.7%). Two deaths were considered possibly related to study drug therapy. One patient experienced bradycardia, acidosis and eventual multi-system organ failure, and the other suffered sepsis and multi-organ failure. There

were 4 other deaths with a remote possibility of being drug related: two occurrences each of heart arrest and sepsis.

ii. Most common non-venous adverse events: Adverse non-venous events were reported in 127 (55.9%) of the patient population. There were 17 (7.5%) events which were considered probably or possibly related to Synercid therapy. The following table presents these events by body system (some patients experienced more than one event):

Body System /Adverse Event	Number (%) of Patients
Digestive system	**7 (3.1)**
Nausea	3 (1.3)
Musculoskeletal system	**4 (1.8)**
Arthralgia	4 (1.8)
Skin & appendages	**4 (1.8)**
Body as a whole	**2 (0.9)**
Cardiovascular system	**3 (1.3)**

It is noted that the safety update tabulation of musculoskeletal reactions for this study presented a total of 5/197 = 2.5% cases of "musculoskeletal syndrome" in study 399. There is no explanation why the total number of patients in this presentation is 197 rather than 227, nor the origin of the additional case.

iii. Venous adverse events: There were 39 patients in the study who had the drug administered by peripheral catheter. Six (15.4%) of these patients reported an adverse venous event.

iv. Events resulting in discontinuation: Eighty-one patients (35.7%) discontinued due to adverse events. Most of these patients died. In addition to the reactions possibly or probably related to therapy in these patients which were described under Deaths above, there were 4 other events which led to treatment discontinuation: one each of hyperesthesia and phlebitis, and two cases of arthralgia.

v. Serious adverse events: There were 10 adverse events (4.4%) classified as serious (other than deaths). Two of these were considered possibly or probably related to study drug treatment: one pseudomembranous enterocolitis and one injection site reaction.

F. Arthralgias/myalgias

The high incidence of myalgias and arthralgias has not been explained by the applicant. A safety board (composition not stated) was consulted by RPR in an effort to understand the pathogenesis of these effects. A number of hypotheses were presented, but none were accepted as likely by the attendees. No predictors were identified though there is a suggestion of higher risk in patients with liver and biliary tract disease. It was agreed that analyses for CPK, aldolase and

serum myoglobin concentrations in affected patients might be useful. Additional suggested tests in those exhibiting these effects were bone scans, EMG, nerve conduction studies and muscle MRI. The applicant does not note any sequelae from the myalgias and arthralgias.

Reviewer's Comment: **Since the patients entered into these studies were so ill, it is difficult to assign any untoward effects (with the exception of the arthralgias and myalgias) to Synercid. No patterns of unexpected adverse events were seen in these studies. With the relatively poor documentation in studies 397, 398C and 399 some toxicities which occurred may not have been noted.**

II. Laboratory Adverse Events in VREF Studies

The following summarizes the laboratory safety data from the VREF studies. Specimens for determination of liver function tests (serum AST, ALT, total and conjugated bilirubin) were taken at baseline, every 3 days during treatment, and at end of treatment. If the patient received home intravenous therapy, the patient had liver function tests performed once a week. If available, results of the following laboratory tests were recorded on the case report form:

Blood chemistry: creatinine, glucose, total protein, albumin, total and conjugated bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), gamma glutamyl transferase (GGT), LDH, calcium, phosphorus, electrolytes (sodium, potassium, chloride, bicarbonate)

Hematology: hemoglobin, hematocrit, total red blood cell (RBC) count, total WBC count with differential, platelet count

Information on coagulation studies was not collected. Abnormal values were to be followed if possible until a return to normal or to baseline occurred.

Note: Attached to this review is Table 5 from study 301, which defines (per sponsor) clinically significant and critical laboratory values.

Study 301

Serious adverse laboratory events occurred in 21 (8.0%) patients of the 263 enrolled. A single serious laboratory adverse event was considered related to study drug (elevated direct and total bilirubin). Two patients had study drug discontinued primarily due to adverse laboratory events; these patients had a variety of blood chemistry abnormalities, including abnormal bilirubin, alkaline phosphatase, SGOT, SGPT and GGT. Neither discontinuation was felt to be due to Synercid therapy. Six patients were discontinued from the study at least partially due to adverse laboratory events. One of these was considered related to study drug (decreased hemoglobin).

The most frequent critically abnormal on-treatment serum chemistry abnormality described was in liver function tests, specifically elevations in conjugated and total bilirubin. Critically abnormal values were defined for these serum chemistries as elevations of greater than 5 times the upper limit of normal; no assessment of attribution to study drug was given. Critical elevations of total bilirubin occurred in 65 (25.4%) patients, and 20 remained abnormal post treatment. Critical elevations of conjugated bilirubin were found in 89 (36.2%) and remained elevated in 21 post-treatment. Critical elevations in other serum chemistries were found in less

than 10% of patients with the exception of elevated BUN (≥35.5 mmol/L) and GGT (more than 10 times the upper limit of normal) which occurred in 24 (9.8%) and 27 (10.9%), respectively.

Critically abnormal hematology values included: depression of neutrophils to <100/cu mm in 17 (6.9%) and remained abnormal post treatment in 1; depression of hemoglobin to less than 8 g/dL in 114 (45.1%) and remained abnormal in 39; and thrombocytopenia (<50,000/cu mm) in 82 (32.4%) which remained abnormal in 22.

Study 398A

Serious adverse laboratory events occurred in 12 (5.5%) patients of the 219 enrolled. Only two episodes of serious laboratory adverse events were considered related to study drug (one pancytopenia and one elevated serum bicarbonate). Six patients had study drug discontinued primarily due to adverse laboratory events; nine patients were discontinued from the study at least partially due to adverse laboratory events. Seven of these patients were thought to have laboratory adverse events possibly or probably related to study drug. Three of these patients displayed liver function abnormalities (bilirubin, SGOT, and/or SGPT). Three others displayed hematologic abnormalities (eosinophils, platelets, hemoglobin, and/or hematocrit). One patient displayed electrolyte abnormalities (carbon dioxide, chloride, sodium).

The most frequent critically abnormal on-treatment serum chemistry abnormality described was in liver function tests, specifically elevations in conjugated and total bilirubin. Critically abnormal values were defined for these serum chemistries as elevations of greater than 5 times the upper limit of normal; no assessment of attribution to study drug was given. Critical elevations of total bilirubin occurred in 45 (22.5%) of patients, and 10 remained abnormal post treatment. Critical elevations of conjugated bilirubin were found in 45 (29.8%) and remained elevated in 9 post-treatment. Critical elevations in other serum chemistries were found in less than 10% of patients with the exception of elevated BUN which occurred in 17 (14%).

Critically abnormal hematology values included: depression of neutrophils to <100/cu mm in 3 (2.8%) and remained abnormal post treatment in 1; depression of hemoglobin to less than 8 g/dL in 19 (16%) which remained abnormal in 15; and thrombocytopenia (<50,000/cu mm) in 37 (31.4%) which remained abnormal in 15.

Study 398B

Serious adverse laboratory events occurred in 23 (4.4%) patients of the 528 enrolled. Only three episodes of serious laboratory adverse events were considered related to study drug (two decreased hemoglobin and one elevated SGOT). Eleven patients had study drug discontinued primarily due to adverse laboratory events; sixteen patients were discontinued from the study at least partially due to adverse laboratory events. Thirteen of these patients were thought to have laboratory adverse events possibly or probably related to study drug. Eight of these patients displayed liver function abnormalities (elevated bilirubin, SGOT, and/or SGPT). Four others displayed hematologic abnormalities (depressed WBC's, hematocrit, hemoglobin and/or red blood cells). One patient displayed elevated BUN and creatinine.

The most frequent critically abnormal on-treatment serum chemistry abnormality described was in liver function tests, specifically elevations in conjugated and total bilirubin. Critically

abnormal values were defined for these serum chemistries as elevations of greater than 5 times the upper limit of normal; no assessment of attribution to study drug was given. Critical elevations of total bilirubin occurred in 117 (24.9%) patients, and 18 remained abnormal post treatment. Critical elevations of conjugated bilirubin were found in 111 (42%) and remained elevated in 17 post-treatment. Critical elevations in other serum chemistries were found in less than 10% of patients with the exception of elevated BUN which occurred in 36 (12.8%).

Study 399

Serious adverse laboratory events occurred in 57 (25.1%) patients of the 227 enrolled. Seventeen episodes of serious laboratory adverse events were considered related to study drug. Three of these patients had multiple (serum chemistry and hematologic) abnormalities, including but not limited to increases in alkaline phosphatase, creatinine, GGT, SGOT, and bilirubin. Seven others had liver function abnormalities (increases in bilirubin, SGOT, SGPT). Seven patients displayed hematologic abnormalities (decreases in WBCs, platelets, hematocrit and/or hemoglobin) and/or increases in creatinine. Thirteen patients had study drug discontinued primarily due to adverse laboratory events. Twelve of these patients were thought to have laboratory adverse events possibly or probably related to study drug. Eight patients displayed liver function abnormalities (increases in bilirubin, SGOT, SGPT). Three patients displayed hematologic abnormalities (decreased WBCs, platelets) and one patient had marginally low serum sodium levels.

The most frequent critically abnormal on-treatment serum chemistry abnormality described was in liver function tests, specifically elevations in conjugated and total bilirubin. Critically abnormal values were defined for these serum chemistries as elevations of greater than 5 times the upper limit of normal; no assessment of attribution to study drug was given. Critical elevations of total bilirubin occurred in 44 (28%) patients, and 16 remained abnormal post treatment. Critical elevations of conjugated bilirubin were found in 14 (16.3%) and remained elevated in 8 post-treatment. Critical elevations in other serum chemistries were found in less than 10% of patients with the exception of elevated BUN (≥35.5 mmol/L) and creatinine (≥440 µmol/L) which occurred in 14.8% and 17.3%, respectively, and elevated GGT (more than 10 times the upper limit of normal) found in 12.9%.

Critically abnormal hematology values included: depression of neutrophils to <100/cu mm in 5 (3.2%) and resolved post treatment; depression of hemoglobin to less than 8 g/dL in 60 (35.9%) and remained abnormal in 11; and thrombocytopenia (<50,000/cu mm) in 59 (35.8%) which remained abnormal in 12.

Reviewer's Note: **The denominators used in the above percentages varied according to the number of patients who had the laboratory test performed. Therefore, the percentages**

shown for each test are not always directly related to the number of patients entering the study.

Safety update dated January 5, 1998

The Safety update did not categorize laboratory adverse events separately. Listed among the adverse safety events for the 1305 patients treated were the following laboratory adverse events (classified by COSTART term):

Hematology:	Anemia	5 patients
	Leukopenia	4 patients
Digestive:	"Liver function test abnormal"	1 patient

III. Comments on Arrhythmias and Drug-Drug Interactions

1. ARRHYTHMIAS

The incidence of cardiac arrhythmias during the course of these three studies was examined. Given the extremely serious nature of these patients' illness, the arrhythmias may be accounted for by their underlying disease process. Overall, cardiovascular adverse events thought to be related to study drug occurred in 2.3% of patients in study 301, 0.5% in study 398A, and 0% in study 399. The available information regarding the occurrence of cardiac arrhythmias during these studies was reviewed.

A. For patients who died, the following listing is of patients with arrhythmias included under adverse events, type of arrhythmia, and attribution.

Study 301	128 deaths	1 ventricular tachycardia - not related
		1 "arrhythmia" - not related
Study 398A	104 deaths	1 ventricular fibrillation - not related
		1 supraventricular tachycardia - not related
		1 "arrhythmia" - not related
		1 atrial fibrillation - not related
Study 398B	278 deaths	1 ventricular arrhythmia - not related
		1 ventricular fibrillation - not related
		1 "arrhythmia" - not related
Study 399	106 deaths	1 bradycardia - possibly related
		2 "arrhythmia" - not related

B. Serious adverse clinical events with an outcome other than death include the following cardiac arrhythmias:

Study 301: 2 episodes of supraventricular tachycardia, 4 episodes of ventricular tachycardia, 10 episodes of bradycardia, 5 episodes of atrial fibrillation/flutter, 2 episodes of ventricular fibrillation, and 1 episode of ventricular extrasystoles; only the extrasystoles were thought to be possibly related to study medication.

Study 398A: 1 episode of supraventricular tachycardia, not related to Synercid.
Study 398B: 6 episodes of bradycardia, 2 episodes of ventricular tachycardia, 1 episode of ventricular fibrillation, and 1 episode of atrial fibrillation; only the ventricular fibrillation was thought to be remotely related to study medication.
Study 399: 2 episodes of "arrhythmias", both unrelated to study drug.

The only tabulation of adverse events available from the Safety update is a listing of the number of patients with adverse events classified by COSTART term. The following arrhythmias were described out of 179 total cardiovascular events: arrhythmia - 9, atrial fibrillation - 3, bradycardia - 9, bundle branch block - 1, heart block - 2, supraventricular tachycardia - 2, ventricular tachycardia - 2 (total of 28 adverse events which were arrhythmias).

The most commonly noted arrhythmia appears to be bradycardia, although a wide variety of atrial and ventricular cardiac arrhythmias was observed. Additionally, in only one instance does it appear that bradycardia was contributory to death. From the characterization provided in the submission, there does not appear to be an unusual number of any specific cardiac arrhythmia during Synercid treatment. It is possible that the occurrence of cardiac arrhythmias in individual patients may be the result of drug-drug interactions with resultant alterations in metabolism of cardioactive medications, as described below.

2. **Drug-Drug Interactions**

Synercid has been shown to inhibit the CYP3A4 isoenzyme of the P450 system. It is possible that medications which are substrates for this isoenzyme may demonstrate enhanced pharmacologic effects as a result of diminished metabolism. The following medications are metabolized by the CYP3A4 isoenzyme:

carbamazepine	cyclosporine	tacrolimus	verapamil
diltiazem	nifedipine	lidocaine	quinidine
amiodarone	midazolam	triazolam	lovastatin
simvastatin	pimozide	cisapride	alprazolam
delavirdine	nevirapine	vinblastine	disopyramide
	astemizole	loratadine	

The best studied drug interaction is Synercid coadministered with cyclosporine. Synercid was administered by intravenous infusion every 8 hours over 4 days in a dose of 7.5 mg/kg of body weight, and cyclosporine was orally administered as a single dose of 300 mg alone and 1.5 hour prior to the fourth dose of Synercid in young healthy male subjects. The results indicate a significant pharmacokinetic interaction between Synercid and cyclosporine. The total AUC for cyclosporine was increased by approximately 60% following administration of Synercid. Peak plasma concentrations of cyclosporine were increased by approximately one-third, and the terminal elimination half-life increased approximately 40%. During Phase 3 clinical trials, several investigators described more difficulty than usual in maintaining therapeutic cyclosporine levels; however, the cyclosporine levels were not systematically monitored and recorded. In light of this

information, cyclosporine levels should be monitored when this drug is given together with Synercid.

No significant effect was found on the protein binding of warfarin when Synercid was added to an *in vitro* system. Although it is considered unlikely that a displacement drug interaction would occur, this possibility should be considered when drugs which are highly protein bound are given with Synercid.

In the Emergency-use studies, patients who received concomitant diltiazem, cyclosporine, tacrolimus, lidocaine, midazolam, or cisapride had incidences of serious adverse non-venous events that were higher (>10 percentage point difference) than those that did not receive those medications. However, when only serious events possibly or probably related were considered, these differences were not seen.

Additional drug interactions which might be predicted to occur include exacerbation of hepatotoxicity or venous irritation when Synercid is coadministered with medications with these adverse event profiles. There are no reports of animal models showing antagonism of other antibiotics with Synercid; checkerboard *in vitro* studies with *S. aureus* (glycopeptides, aminoglycosides, quinolones, chloramphenicol, tetracycline/doxycycline) and with VREF (gentamicin, doxycycline, or chloramphenicol) are not suggestive of such a phenomenon.

Reviewers Note:
During the Phase 3 comparative studies, patients who received diltiazem, cisapride, or midazolam concomitantly with Synercid had higher incidences (>10 percentage point difference) of on-treatment adverse non-venous events than those who did not receive them. However, for those events considered related the difference persisted only for cisapride.

IV. Conclusions:

Approval for Synercid in VREF is not prohibited by safety considerations. While the incidences of arthralgia and myalgia are high and unexplained, these events appear to be reversible, and the potential for Synercid to act against pathogens which are resistant to vancomycin outweighs the concern about these effects.

No firm conclusions can be drawn concerning liver toxicity possibly associated with Synercid administration. (See safety review of NDA 50-748 dated February 2, 1998.) It is well-established that Synercid causes venous irritation. (See above referenced review.) As noted above, possible drug-drug interactions concerning Synercid have not been adequately studied.

Further, it is noted that in the best documented study (301), 99.2% of the patient population experienced some adverse event without regard to attribution.

Although approval under the Accelerated Approval regulations is the action taken for Synercid in the treatment of VREF infections, additional safety information regarding the use of Synercid is necessary. The safety update report is lacking in detail. Therefore, the safety data since the NDA cutoff date (i.e., January 8, 1996) have not been well presented, organized, or analyzed. The following items to be requested of the applicant are to address the deficiencies in the safety information. Safety information from the NDA cutoff date to the present should be included.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submissions. Tables comparing adverse reactions from the original NDA submission (data cutoff date: January 8, 1996) versus subsequent data will facilitate review.

2. Retabulation of drop-outs and deaths with new drop-outs and deaths identified.

3. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event, if the event was evaluated as possibly or probably related to study drug.

4. Tabulations for the venous adverse events, presented by indication, with information on whether the events were reversible and how many led to drug discontinuation.

5. Concerning the VREF studies, tabulations should be presented concerning the underlying disease status of the patients who died while on Synercid therapy.

In addition, the following should be requested of the applicant:

1. Summary of worldwide experience on the safety of Synercid.

2. Details of any significant changes or findings in the safety profile of Synercid.

3. Provide a definition of the terms "aggravation reaction" and "musculoskeletal syndrome" as used in the safety update of January 5, 1998.

4. In the confirmatory (Phase 4) clinical study, the analyses suggested by the safety board convened on the subject of arthralgias and myalgias should be conducted. These would include, but are not limited to, analyses for CPK, aldolase and serum myoglobin concentrations in affected patients, EMG, and nerve conduction studies . Information on the reversibility of the arthralgias and myalgias found to date should also be submitted, as well as any animal data which may suggest a pathophysiology for these phenomena.

5. Studies should be initiated during the Phase 4 clinical trial which are designed to elucidate the mechanism for the hepatic changes (bilirubin) seen in the clinical studies performed so far. Tabulations for bilirubin abnormalities seen to date should be presented by indication, to include mean, median and greatest change in bilirubin, as well as information on resolution of the abnormality (e.g., time to return to baseline).

6. Additional studies on drug-drug interactions should be performed, either as part of the Phase 4 clinical trial or as new studies.

/S/
Susan Thompson, M.D.

/S/
David C. Bostwick

Attachment
cc:Orig NDA
HFD-340
HFD-520
HFD-520/DepDir/Gavrilovich
HFD-520/Clin/Rakowsky
HFD-520/Clin/SThompson
HFD-520/Clin/Bostwick
HFD-520/TClin/Roberts 8/21/98
HFD-520/ProjMgr/Dillon-Parker
HFD-520/Micro/Marsik
HFD-520/Chem/Timper
HFD-240

Concurrence only: HFD-520/DivDir/Chikami /S/ 8/25/98