Synercid® I.V.

(quinupristin and dalfopristin for injection)

One of **Synercid's** approved indications is for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. **Synercid** has been approved for marketing in the United States for this indication under FDA's accelerated approval regulations that allow marketing of products for use in life-threatening conditions when other therapies are not available. Approval of drugs for marketing under these regulations is based upon a demonstrated effect on a surrogate endpoint that is likely to predict clinical benefit.

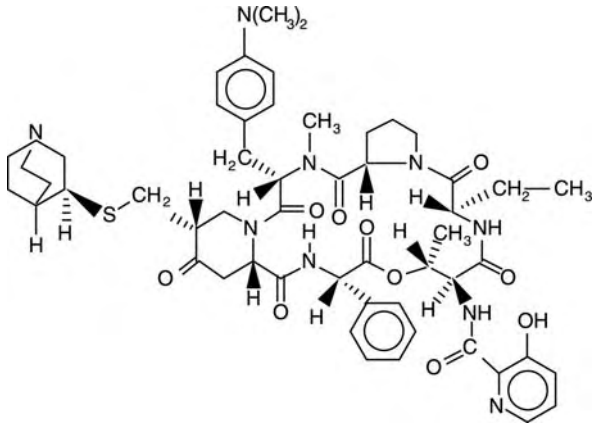
Approval of this indication is based upon **Synercid's** ability to clear VREF from the bloodstream, with clearance of bacteremia considered to be a surrogate endpoint. There are no results from well-controlled clinical studies that confirm the validity of this surrogate marker. However, a study to verify the clinical benefit of therapy with **Synercid** on traditional clinical endpoints (such as cure of the underlying infection) is presently underway.

DESCRIPTION

Synercid® (quinupristin and dalfopristin powder for injection) I.V., a streptogramin antibacterial agent for intravenous administration, is a sterile lyophilized formulation of two semisynthetic pristinamycin derivatives, quinupristin (derived from pristinamycin I) and dalfopristin (derived from pristinamycin IIA) in the ratio of 30:70 (w/w).

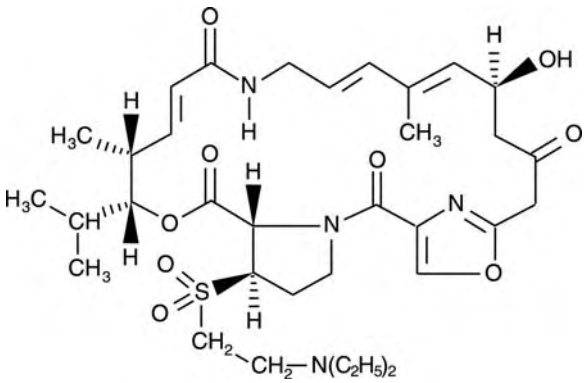
Quinupristin is a white to very slightly yellow, hygroscopic powder. It is a combination of three peptide macrolactones. The main component of quinupristin (>88.0%) has the following chemical name: N-[(6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-[[(3*S*)-3-quinuclidinylthio] methyl]-12*H*-pyrido[2,1-*f*]pyrrolo-[2,1-*l*][1,4,7,10,13,16] oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide.

The main component of quinupristin has an empirical formula of $C_{53}H_{67}N_9O_{10}S$, a molecular weight of 1022.24 and the following structural formula:



Dalfopristin is a slightly yellow to yellow, hygroscopic, powder. The chemical name for dalfopristin is: (3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-[[2-(diethylamino)ethyl]sulfonyl]-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]-dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone.

Dalfopristin has an empirical formula of $C_{34}H_{50}N_4O_9S$, a molecular weight of 690.85 and the following structural formula:



CLINICAL PHARMACOLOGY

Pharmacokinetics: Quinupristin and dalfopristin are the main active components circulating in plasma in human subjects. Quinupristin and dalfopristin are converted to several active major metabolites: two conjugated metabolites for quinupristin (one with glutathione and one with cysteine) and one non-conjugated metabolite for dalfopristin (formed by drug hydrolysis).

Pharmacokinetic profiles of quinupristin and dalfopristin in combination with their metabolites were determined using a bioassay following multiple 60-minute infusions of **Synercid** in two groups of healthy young adult male volunteers. Each group received 7.5 mg/kg of **Synercid** intravenously q12h or q8h for a total of 9 or 10 doses, respectively. The pharmacokinetic parameters were proportional with q12h and q8h dosing; those of the q8h regimen are shown in the following table:

Mean Steady-State Pharmacokinetic Parameters of Quinupristin and Dalfopristin in Combination with their Metabolites (± SD[1]) (dose = 7.5 mg/kg q8h; n=10)

	C_{max}[2] (µg/mL)	AUC[3] (µg.h/mL)	$t_{1/2}$[4] (hr)
Quinupristin and metabolites	3.20 ± 0.67	7.20 ± 1.24	3.07 ± 0.51
Dalfopristin and metabolite	7.96 ± 1.30	10.57 ± 2.24	1.04 ± 0.20

[1] SD= Standard Deviation

[2] C_{max} = Maximum drug plasma concentration

[3] AUC = Area under the drug plasma concentration-time curve

[4] $t_{1/2}$ = Half-life

The clearances of unchanged quinupristin and dalfopristin are similar (0.72 L/h/kg), and the steady-state volume of distribution for quinupristin is 0.45 L/kg and for dalfopristin is 0.24 L/kg. The elimination half-life of quinupristin and dalfopristin is approximately 0.85 and 0.70 hours, respectively.

The protein binding of **Synercid** is moderate.

Penetration of unchanged quinupristin and dalfopristin in noninflammatory blister fluid corresponds to about 19% and 11% of that estimated in plasma, respectively. The penetration into blister fluid of quinupristin and dalfopristin in combination with their major metabolites was in total approximately 40% compared to that in plasma.

In vitro, the transformation of the parent drugs into their major active metabolites occurs by non-enzymatic reactions and is not dependent on cytochrome-P450 or glutathione-transferase enzyme activities.

Synercid has been shown to be a major inhibitor (*in vitro* inhibits 70% cyclosporin A biotransformation at 10 µg/mL of **Synercid**) of the activity of cytochrome P450 3A4 isoenzyme. (See **WARNINGS**.)

Synercid can interfere with the metabolism of other drug products that are associated with QTc prolongation. However, electrophysiologic studies confirm that **Synercid** does not itself induce QTc prolongation. (See **WARNINGS**.)

Fecal excretion constitutes the main elimination route for both parent drugs and their metabolites (75 to 77% of dose). Urinary excretion accounts for approximately 15% of the quinupristin and 19% of the dalfopristin dose. Preclinical data in rats have demonstrated that approximately 80% of the dose is excreted in the bile and suggest that in man, biliary excretion is probably the principal route for fecal elimination.

Special Populations

Elderly: The pharmacokinetics of quinupristin and dalfopristin were studied in a population of elderly individuals (range 69 to 74 years). The pharmacokinetics of the drug products were not modified in these subjects.

Gender: The pharmacokinetics of quinupristin and dalfopristin are not modified by gender.

Renal Insufficiency: In patients with creatinine clearance 6 to 28 mL/min, the AUC of quinupristin and dalfopristin in combination with their major metabolites increased about 40% and 30%, respectively.

In patients undergoing Continuous Ambulatory Peritoneal Dialysis, dialysis clearance for quinupristin, dalfopristin and their metabolites is negligible. The plasma AUC of unchanged quinupristin and dalfopristin increased about 20% and 30%, respectively. The high molecular weight of both components of **Synercid** suggests that it is unlikely to be removed by hemodialysis.

Hepatic Insufficiency: In patients with hepatic dysfunction (Child-Pugh scores A and B), the terminal half-life of quinupristin and dalfopristin was not modified. However, the AUC of quinupristin and dalfopristin in combination with their major metabolites increased about 180% and 50%, respectively. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**.)

Obesity (body mass index $\geq$30): In obese patients the C_{max} and AUC of quinupristin increased about 30% and those of dalfopristin about 40%.

Pediatric Patients: The pharmacokinetics of **Synercid** in patients less than 16 years of age have not been studied.

Microbiology: The streptogramin components of **Synercid**, quinupristin and dalfopristin, are present in a ratio of 30 parts quinupristin to 70 parts dalfopristin. These two components act synergistically so that **Synercid's** microbiologic *in vitro* activity is greater than that of the components individually. Quinupristin's and dalfopristin's metabolites also contribute to the antimicrobial activity of **Synercid**. *In vitro* synergism of the major metabolites with the complementary parent compound has been demonstrated.

Synercid is bacteriostatic against *Enterococcus faecium* and bactericidal against strains of methicillin-susceptible and methicillin-resistant staphylococci.

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

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

In vitro combination testing of **Synercid** with prototype drugs of the following classes: aminoglycosides (gentamicin), ß-lactams (cefepime, ampicillin, and amoxicillin), glycopeptides (vancomycin), quinolones (ciprofloxacin), tetracyclines (doxycycline) and also chloramphenicol against enterococci and staphylococci did not show antagonism.

The mode of action differs from that of other classes of antibacterial agents such as ß-lactams, aminoglycosides, glycopeptides, quinolones, macrolides, lincosamides and tetracyclines. There is no cross resistance between **Synercid** and these agents when tested by the minimum inhibitory concentration (MIC) method.

In non-comparative studies, emerging resistance to **Synercid** during treatment of VREF infections occurred. Resistance to **Synercid** is associated with resistance to both components (*i.e.*, quinupristin and dalfopristin).

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

Aerobic gram-positive microorganisms

Enterococcus faecium (**Vancomycin-resistant and multi-drug resistant strains only**)

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pyogenes

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

The following *in vitro* data are available, **but their clinical significance is unknown**.

The combination of quinupristin and dalfopristin (**Synercid**) exhibits *in vitro* minimum inhibitory concentrations (MIC's) of ≤1.0 µg/mL against most (≥90%) isolates of the following microorganisms; however, the safety and effectiveness of **Synercid** in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Corynebacterium jeikeium

Staphylococcus aureus (methicillin-resistant strains)

Staphylococcus epidermidis (including methicillin-resistant strains)

Streptococcus agalactiae

SUSCEPTIBILITY TESTING

Dilution Techniques

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

For Susceptibility Testing of *Enterococcus faecium*, *Staphylococcus* spp., and *Streptococcus* spp. (excluding *Streptococcus pneumoniae*)[a.]

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

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

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

Quality Control

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

Microorganism (ATCC® #)	MIC (µg/mL)
Enterococcus faecalis (29212)	2.0 to 8.0
Staphylococcus aureus (29213)	0.25 to 1.0

Diffusion Techniques

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

For Susceptibility Testing of *Enterococcus faecium*, *Staphylococcus* spp., and *Streptococcus* spp. (excluding *Streptococcus pneumoniae*)[b.]

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

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

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

Quality Control

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

Microorganism (ATCC® #)	Zone Diameter Range (mm)
Staphylococcus aureus (25923)	21 to 28

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

INDICATIONS AND USAGE

Synercid is indicated in adults for the treatment of the following infections when caused by susceptible strains of the designated microorganisms.

Vancomycin-resistant *Enterococcus faecium* (VREF)

Synercid is indicated for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. (See **CLINICAL STUDIES**.)

One of **Synercid's** approved indications is for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. **Synercid** has been approved for marketing in the United States for this indication under FDA's accelerated approval regulations that allow marketing of products for use in life-threatening conditions when other therapies are not available. Approval of

drugs for marketing under these regulations is based upon a demonstrated effect on a surrogate endpoint that is likely to predict clinical benefit.
Approval of this indication is based upon **Synercid's** ability to clear VREF from the bloodstream, with clearance of bacteremia considered to be a surrogate endpoint. There are no results from well-controlled clinical studies that confirm the validity of this surrogate marker. However, a study to verify the clinical benefit of therapy with **Synercid** on traditional clinical endpoints (such as cure of the underlying infection) is presently underway.
Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin susceptible) or *Streptococcus pyogenes*. (See **CLINICAL STUDIES**.)

CONTRAINDICATIONS
Synercid is contraindicated in patients with known hypersensitivity to **Synercid**, or with prior hypersensitivity to other streptogramins (*e.g.*, pristinamycin or virginiamycin).

WARNINGS
Drug Interactions: *In vitro* drug interaction studies have demonstrated that **Synercid** significantly inhibits cytochrome P450 3A4 metabolism of cyclosporin A, midazolam, nifedipine and terfenadine. In addition, 24 subjects given **Synercid** 7.5 mg/kg q8h for 2 days and 300 mg of cyclosporine on day 3 showed an increase of 63% in the AUC of cyclosporine, an increase of 30% in the C_{max} of cyclosporine, a 77% increase in the $t_{1/2}$ of cyclosporine, and, a decrease of 34% in the clearance of cyclosporine. **Therapeutic level monitoring of cyclosporine should be performed when cyclosporine must be used concomitantly with Synercid.**
It is reasonable to expect that the concomitant administration of Synercid and other drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may likely result in increased plasma concentrations of these drugs that could increase or prolong their therapeutic effect and/or increase adverse reactions. (See Table below.) Therefore, coadministration of Synercid with drugs which are cytochrome P450 3A4 substrates and possess a narrow therapeutic window requires caution and monitoring of these drugs (*e.g.*, cyclosporine), whenever possible. Concomitant medications metabolized by the cytochrome P450 3A4 enzyme system that may prolong the QTc interval should be avoided.
Concomitant administration of **Synercid** and nifedipine (repeated oral doses) and midazolam (intravenous bolus dose) in healthy volunteers led to elevated plasma concentrations of these drugs. The C_{max} increased by 18% and 14% (median values) and the AUC increased by 44% and 33% for nifedipine and midazolam, respectively.
Table of Selected Drugs That Are Predicted to Have Plasma Concentrations Increased by **Synercid** +
Antihistamines: astemizole, terfenadine
Anti-HIV (NNRTIs and Protease inhibitors): delavirdine, nevirapine, indinavir, ritonavir
Antineoplastic agents: vinca alkaloids (*e.g.*, vinblastine), docetaxel, paclitaxel
Benzodiazepines: midazolam, diazepam
Calcium channel blockers: dihydropyridines (*e.g.*, nifedipine), verapamil, diltiazem
Cholesterol-lowering agents: HMG-CoA reductase inhibitors (*e.g.*, lovastatin)
GI motility agents: cisapride
Immunosuppressive agents: cyclosporine, tacrolimus
Steroids: methylprednisolone
Other: carbamazepine, quinidine, lidocaine, disopyramide
+ This list of drugs is not all inclusive.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including **Synercid**, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS
General: *Venous Irritation:* Following completion of a peripheral infusion, the vein should be flushed with 5% Dextrose in Water solution to minimize venous irritation. **DO NOT FLUSH** with saline or heparin **after Synercid** administration because of incompatibility concerns.
If moderate to severe venous irritation occurs following peripheral administration of **Synercid** diluted in 250 mL of Dextrose 5% in water, consideration should be given to increasing the infusion volume to 500 or 750 mL, changing the infusion site, or infusing by a peripherally inserted central catheter (PICC) or a central venous catheter. In clinical trials, concomitant administration of hydrocortisone or diphenhydramine did not appear to alleviate venous pain or inflammation.
Rate of Infusion: In animal studies toxicity was higher when **Synercid** was administered as a bolus compared to slow infusion. However, the safety of an intravenous bolus of **Synercid** has not been studied in humans. Clinical trial experience has been exclusively with an intravenous duration of 60 minutes and, thus, other infusion rates cannot be recommended.
Arthralgias/Myalgias: Episodes of arthralgia and myalgia, some severe, have been reported in patients treated with **Synercid**. In some patients, improvement has been noted with a reduction in dose frequency to q12h. In those patients available for follow-up, treatment discontinuation has been followed by resolution of symptoms. The etiology of these myalgias and arthralgias is under investigation.
Superinfections: The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.
Hyperbilirubinemia: Elevations of total bilirubin greater than 5 times the upper limit of normal were noted in approximately 25% of patients in the non-comparative studies. (See **CLINICAL STUDIES: Non-Comparative Trials.**) In some patients, isolated hyperbilirubinemia (primarily conjugated) can occur during treatment, possibly resulting from competition between **Synercid** and bilirubin for excretion. Of note, in the comparative trials, elevations in ALT and AST occurred at a similar frequency in both the **Synercid** and comparator groups.
Information for Patients:
Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.
Drug Interactions: *In vitro* drug interaction studies have shown that **Synercid** significantly inhibits cytochrome P450 3A4. (See **WARNINGS**.)
Synercid does not significantly inhibit human cytochrome P450 1A2, 2A6, 2C9, 2C19, 2D6, or 2E1. Therefore, clinical interactions with drugs metabolized by these cytochrome P450 isoenzymes are not expected.

A drug interaction between **Synercid** and digoxin cannot be excluded but is unlikely to occur via CYP3A4 enzyme inhibition. **Synercid** has shown *in vitro* activity (MICs of 0.25 mcg/mL when tested on two strains) against *Eubacterium lentum*. Digoxin is metabolized in part by bacteria in the gut and as such, a drug interaction based on **Synercid's** inhibition of digoxin's gut metabolism (by *Eubacterium lentum*) may be possible.
In vitro combination testing of **Synercid** with aztreonam, cefotaxime, ciprofloxacin, and gentamicin, against *Enterobacteriaceae* and *Pseudomonas aeruginosa* did not show antagonism.
In vitro combination testing of **Synercid** with prototype drugs of the following classes: aminoglycosides (gentamicin), ß-lactams (cefepime, ampicillin, and amoxicillin), glycopeptides (vancomycin), quinolones (ciprofloxacin), tetracyclines (doxycycline) and also chloramphenicol against enterococci and staphylococci did not show antagonism.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been conducted with **Synercid**. Five genetic toxicity tests were performed. **Synercid**, dalfopristin, and quinupristin were tested in the bacterial reverse mutation assay, the Chinese hamster ovary cell HGPRT gene mutation assay, the unscheduled DNA synthesis assay in rat hepatocytes, the Chinese hamster ovary cell chromosome aberration assay, and the mouse micronucleus assay in bone marrow. Dalfopristin was associated with the production of structural chromosome aberrations when tested in the Chinese hamster ovary cell chromosome aberration assay. **Synercid** and quinupristin were negative in this assay. **Synercid**, dalfopristin, and quinupristin were all negative in the other four genetic toxicity assays.
No impairment of fertility or perinatal/postnatal development was observed in rats at doses up to 12 to 18 mg/kg (approximately 0.3 to 0.4 times the human dose based on body-surface area).
Pregnancy: Teratogenic Effects: *Pregnancy Category B:* Reproductive studies have been performed in mice at doses up to 40 mg/kg/day (approximately half the human dose based on body-surface area), in rats at doses up to 120 mg/kg/day (approximately 2.5 times the human dose based on body-surface area), and in rabbits at doses up to 12 mg/kg/day (approximately half the human dose based on body-surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to **Synercid**.
There are, however, no adequate and well-controlled studies with **Synercid** in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: In lactating rats, **Synercid** was excreted in milk. It is not known whether **Synercid** is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when **Synercid** is administered to a nursing woman.
Hepatic Insufficiency: Following a single 1-hour infusion of **Synercid** (7.5 mg/kg) to patients with hepatic insufficiency, plasma concentrations were significantly increased. (See **CLINICAL PHARMACOLOGY: Special Populations**.) However, the effect of dose reduction or increase in dosing interval on the pharmacokinetics of **Synercid** in these patients has not been studied. Therefore, no recommendations can be made at this time regarding the appropriate dose modification.
Pediatric Use: Synercid has been used in a limited number of pediatric patients under emergency-use conditions at a dose of 7.5 mg/kg q8h or q12h. However, the safety and effectiveness of **Synercid** in patients under 16 years of age have not been established.
Geriatric Use: In phase 3 comparative trials of **Synercid**, 37% of patients (n=404) were ≥65 years of age, of which 145 were ≥75 years of age. In the phase 3 non-comparative trials, 29% of patients (n=346) were ≥65 years of age, of which 112 were ≥75 years of age. There were no apparent differences in the frequency, type, or severity of related adverse reactions including cardiovascular events between elderly and younger individuals.

ADVERSE REACTIONS

The safety of **Synercid** was evaluated in 1099 patients enrolled in 5 comparative clinical trials. Additionally, 4 non-comparative clinical trials (3 prospective and 1 retrospective in design) were conducted in which 1199 patients received **Synercid** for infections due to Gram-positive pathogens for which no other treatment option was available. In non-comparative trials, the patients were severely ill, often with multiple co-morbidities or physiological impairments, and may have been intolerant to or failed other antibacterial therapies.

COMPARATIVE TRIALS

ADVERSE REACTION SUMMARY — ALL COMPARATIVE STUDIES

Safety data are available from five comparative clinical studies (n= 1099 **Synercid**; n= 1095 comparator). One of the deaths in the comparative studies was assessed as possibly related to **Synercid**. The most frequent reasons for discontinuation due to drug-related adverse reactions were as follows:

% of patients discontinuing therapy by reaction type

Type	Synercid	Comparator
Venous	9.2	2.0
Non-venous	9.6	4.3
-Rash	1.0	0.5
-Nausea	0.9	0.6
-Vomiting	0.5	0.5
-Pain	0.5	0.0
-Pruritus	0.5	0.3

CLINICAL REACTIONS — ALL COMPARATIVE STUDIES

Adverse reactions with an incidence of ≥1% and possibly or probably related to **Synercid** administration include:

Adverse Reactions	% of patients with adverse reactions	
	Synercid	Comparator
Inflammation at infusion site	42.0	25.0
Pain at infusion site	40.0	23.7
Edema at infusion site	17.3	9.5
Infusion site reaction	13.4	10.1
Nausea	4.6	7.2
Thrombophlebitis	2.4	0.3
Diarrhea	2.7	3.2
Vomiting	2.7	3.8
Rash	2.5	1.4
Headache	1.6	0.9
Pruritus	1.5	1.1
Pain	1.5	0.1

Additional adverse reactions that were possibly or probably related to **Synercid** with an incidence less than 1% within each body system are listed below:

Body as a Whole: abdominal pain, worsening of underlying illness, allergic reaction, chest pain, fever, infection;
Cardiovascular: palpitation, phlebitis;
Digestive: constipation, dyspepsia, oral moniliasis, pancreatitis, pseudomembranous enterocolitis, stomatitis;
Metabolic: gout, peripheral edema;
Musculoskeletal: arthralgia, myalgia, myasthenia;
Nervous: anxiety, confusion, dizziness, hypertonia, insomnia, leg cramps, paresthesia, vasodilation;

Respiratory: dyspnea, pleural effusion;
Skin and Appendages: maculopapular rash, sweating, urticaria;
Urogenital: hematuria, vaginitis

CLINICAL REACTIONS — SKIN AND SKIN STRUCTURE STUDIES

In two of the five comparative clinical trials **Synercid** (n=450) and comparator regimens (*e.g.*, oxacillin/vancomycin or cefazolin/vancomycin; n=443) were studied for safety and efficacy in the treatment of complicated skin and skin structure infections. The adverse event profile seen in the **Synercid** patients in these two studies differed significantly from that seen in the other comparative studies. What follows is safety data from these two studies.

Discontinuation of therapy was most frequently due to the following drug related events:

	% of patients discontinuing therapy by reaction type	
Type	**Synercid**	**Comparator**
Venous	12.0	2.0
Non-venous	11.8	4.0
-Rash	2.0	0.9
-Nausea	1.1	0.0
-Vomiting	0.9	0.0
-Pain	0.9	0.0
-Pruritus	0.9	0.5

Venous adverse events were seen predominately in patients who had peripheral infusions. The most frequently reported venous and non-venous adverse reactions possibly or probably related to study drug were:

	% of patients with adverse reactions	
	Synercid	**Comparator**
Venous	68.0	32.7
-Pain at infusion site	44.7	17.8
-Inflammation at infusion site	38.2	14.7
-Edema at infusion site	18.0	7.2
-Infusion site reaction	11.6	3.6
Non-venous	24.7	13.1
-Nausea	4.0	2.0
-Vomiting	3.7	1.0
-Rash	3.1	1.3
-Pain	3.1	0.2

There were eight (1.7%) episodes of thrombus or thrombophlebitis in the **Synercid** arms and none in the comparator arms.

LABORATORY EVENTS-ALL COMPARATIVE STUDIES

The following table shows the number (%) of patients exhibiting laboratory values above or below the clinically relevant "critical" values during treatment phase (with an incidence of 0.1% or greater in either treatment group).

Parameter	Critically High or Low Value	Synercid Critically High or Low	Comparator Critically High or Low
AST	> 10 x ULN	9 (0.9)	2 (0.2)
ALT	> 10 x ULN	4 (0.4)	4 (0.4)
Total Bilirubin	> 5 x ULN	9 (0.9)	2 (0.2)
Conjugated Bilirubin	> 5 x ULN	29 (3.1)	12 (1.3)
LDH	> 5 x ULN	10 (2.6)	8 (2.1)
Alk Phosphatase	> 5 x ULN	3 (0.3)	7 (0.7)
Gamma-GT	> 10 x ULN	19 (1.9)	10 (1.0)
CPK	> 10 x ULN	6 (1.6)	5 (1.4)
Creatinine	≥ 440 µmoL/L	1 (0.1)	1 (0.1)
BUN	≥ 35.5 mmoL/L	2 (0.3)	9 (1.2)
Blood Glucose	> 22.2 mmoL/L	11 (1.3)	11 (1.3)
	< 2.2 mmoL/L	1 (0.1)	1 (0.1)
Bicarbonates	> 40 mmoL/L	2 (0.3)	3 (0.5)
	< 10 mmoL/L	3 (0.5)	3 (0.5)
CO_2	> 50 mmoL/L	0 (0.0)	0 (0.0)
	< 15 mmoL/L	1 (0.2)	0 (0.0)
Sodium	> 160 mmoL/L	0 (0.0)	0 (0.0)
	< 120 mmoL/L	5 (0.5)	3 (0.3)
Potassium	> 6.0 mmoL/L	3 (0.3)	6 (0.6)
	< 2.0 mmoL/L	0 (0.0)	1 (0.1)
Hemoglobin	< 8 g/dL	25 (2.6)	16 (1.6)
Hematocrit	> 60%	2 (0.2)	0 (0.0)
Platelets	> 1,000,000/mm^3	2 (0.2)	2 (0.2)
	< 50,000/mm^3	6 (0.6)	7 (0.7)

NON-COMPARATIVE TRIALS

CLINICAL ADVERSE REACTIONS

Approximately one-third of patients discontinued therapy in these trials due to adverse events. However, the discontinuation rate due to adverse reactions assessed by the investigator as possibly or probably related to **Synercid** therapy was approximately 5.0%.

There were three prospectively designed non-comparative clinical trials in patients (n = 972) treated with **Synercid**. One of these studies (301), had more complete documentation than the other two (398A and 398B). The most common events probably or possibly related to therapy were:

Adverse Reactions	% of patients with adverse reaction Study 301	Study 398A	Study 398B
Arthralgia	7.8	5.2	4.3
Myalgia	5.1	0.95	3.1
Arthralgia and Myalgia	7.4	3.3	6.8
Nausea	3.8	2.8	4.9

The percentage of patients who experienced severe related arthralgia and myalgia was 3.3% and 3.1%, respectively. The percentage of patients who discontinued treatment due to related arthralgia and myalgia was 2.3% and 1.8%, respectively.

LABORATORY EVENTS

The most frequently observed abnormalities in laboratory studies were in total and conjugated bilirubin, with increases greater than 5 times upper limit of normal, irrespective of relationship to **Synercid**, reported in 25.0% and 34.6% of patients, respectively. The percentage of patients who discontinued treatment due to increased total and conjugated bilirubin was 2.7% and 2.3%, respectively. Of note, 46.5% and 59.0% of patients had high baseline total and conjugated bilirubin levels before study entry.

OTHER

Serious adverse reactions in clinical trials, including non-comparative studies, considered possibly or probably related to **Synercid** administration with an incidence <0.1% include: acidosis, anaphylactoid reaction, apnea, arrhythmia, bone pain, cerebral hemorrhage, cerebrovascular accident, coagulation disorder, convulsion, dysautonomia, encephalopathy, grand mal convulsion, hemolysis, hemolytic anemia, heart arrest, hepatitis, hypoglycemia, hyponatremia, hypoplastic anemia, hypoventilation, hypovolemia, hypoxia, jaundice, mesenteric arterial occlusion, neck rigidity, neuropathy, pancytopenia, paraplegia, pericardial effusion, pericarditis, respiratory distress syndrome, shock, skin ulcer, supraventricular tachycardia, syncope, tremor, ventricular extrasystoles and ventricular fibrillation. Cases of hypotension and gastrointestinal hemorrhage were reported in less than 0.2% of patients.

Post-marketing Experiences: In addition to adverse events reported from clinical trials, reports of angioedema and anaphylactic shock have been identified during post approval use of **Synercid**.

OVERDOSAGE

There are four reports of patients receiving **Synercid** doses at up to three times that recommended (7.5 mg/kg). No adverse events were considered possibly or probably related to **Synercid** overdose. Signs of acute overdosage may include dyspnea, emesis, tremors, and ataxia as seen in animals given extremely high doses (50 mg/kg) of **Synercid**. Patients who receive an overdose should be carefully observed and given supportive treatment. **Synercid** is not removed by peritoneal dialysis or by hemodialysis.

DOSAGE AND ADMINISTRATION

Synercid should be administered by intravenous infusion in 5% Dextrose in Water solution over a 60-minute period. (See **WARNINGS**.) The recommended dosage for the treatment of infections is described in the table below. An infusion pump or device may be used to control the rate of infusion. If necessary, central venous access (*e.g.*, PICC) can be used to administer **Synercid** to decrease the incidence of venous irritation.

	Dose
Vancomycin-Resistant *Enterococcus faecium*	7.5 mg/kg q8h
Complicated Skin and Skin Structure Infection	7.5 mg/kg q12h

The minimum recommended treatment duration for Complicated Skin and Skin Structure Infections is seven days. For Vancomycin-Resistant *Enterococcus faecium* infection, the treatment duration should be determined based on the site and severity of the infection.

Special Populations: *Elderly:* No dosage adjustment of **Synercid** is required for use in the elderly. (See

CLINICAL PHARMACOLOGY: Pharmacokinetics and **PRECAUTIONS: Geriatric Use**.)
Renal Insufficiency: No dosage adjustment of **Synercid** is required for use in patients with renal impairment or patients undergoing peritoneal dialysis. (See **CLINICAL PHARMACOLOGY: Pharmacokinetics**.)
Hepatic Insufficiency: Data from clinical trials of **Synercid** suggest that the incidence of adverse effects in patients with chronic liver insufficiency or cirrhosis was comparable to that in patients with normal hepatic function. Pharmacokinetic data in patients with hepatic cirrhosis (Child Pugh A or B) suggest that dosage reduction may be necessary but exact recommendations cannot be made at this time. (See **CLINICAL PHARMACOLOGY: Special Populations** and **PRECAUTIONS: General:** *Hepatic Insufficiency* sections.)
Pediatric Patients (less than 16 years of age): Based on a limited number of pediatric patients treated under emergency-use conditions, no dosage adjustment of **Synercid** is required. (See **PRECAUTIONS: Pediatric Use**.)

Preparation and administration of solution:
1. Reconstitute the 500 mg single dose vial by slowly adding 5 mL of 5% Dextrose in Water or Sterile Water for injection.
Reconstitute the 600 mg single dose vial by slowly adding 6 mL of 5% Dextrose in Water or Sterile Water for injection.
2. **GENTLY** swirl the vial by manual rotation without shaking to ensure dissolution of contents while **LIMITING FOAM FORMATION**.
3. Allow the solution to sit for a few minutes until all the foam has disappeared. The resulting solution should be clear. Vials reconstituted in this manner will give a solution of 100 mg/mL. **CAUTION: FURTHER DILUTION REQUIRED BEFORE INFUSION**.
4. According to the patient's weight, the reconstituted **Synercid solution** should be added to 250 mL of 5% Dextrose solution. An infusion volume of 100 mL may be used for central line infusions.
5. If moderate to severe venous irritation occurs following peripheral administration of **Synercid** diluted in 250 mL of Dextrose 5% in water, consideration should be given to increasing the infusion volume to 500 or 750 mL, changing the infusion site, or infusing by a peripherally inserted central catheter (PICC) or a central venous catheter.
6. The desired dose should be administered by intravenous infusion over 60 minutes.
NOTE: As for other parenteral drug products, **Synercid** should be inspected visually for particulate matter prior to administration.

COMPATIBILITY:
DO NOT DILUTE WITH SALINE SOLUTIONS BECAUSE SYNERCID IS NOT COMPATIBLE WITH THESE AGENTS. Synercid should not be mixed with, or physically added to, other drugs except for the following drugs where compatibility by Y-site injection has been established:

Y-Site Injection Compatibility of Synercid at 2 mg/mL Concentration

Admixture and Concentration	**IV Infusion Solutions for Admixture**
Aztreonam 20 mg/mL	D5W
Ciprofloxacin 1 mg/mL	D5W
Fluconazole 2 mg/mL	Used as the undiluted solution
Haloperidol 0.2 mg/mL	D5W
Metoclopramide 5 mg/mL	D5W
Potassium Chloride 40 mEq/L	D5W

D5W = 5% Dextrose Injection

If **Synercid** is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.
With intermittent infusion of **Synercid** and other drugs through a common intravenous line, the line should be flushed before and after administration with 5% Dextrose in Water solution.
Stability and Storage: Before Reconstitution: The unopened vials should be stored in a refrigerator at 2 to 8ºC (36 to 46ºF).
Reconstituted and Infusions Solutions: Because **Synercid** contains no antibacterial preservative, it should be reconstituted under strict aseptic conditions (*e.g.*, Laminar Air Flow Hood). The reconstituted solution should be diluted within 30 minutes. Vials are for single use. The storage time of the diluted solution should be as short as possible to minimize the risk of microbial contamination. Stability of the diluted solution prior to the infusion is established as 5 hours at room temperature or 54 hours if stored under refrigeration 2 to 8ºC (36 to 46ºF). The solution should not be frozen.

HOW SUPPLIED
Synercid is supplied as a sterile lyophilized pyrogen-free preparation in single-dose 10 mL type I glass vials with gray elastomeric closure, and aluminum seal with a dark blue flip-off cap for the 500 mg vial and a red flip-off cap for the 600 mg vial.

NDC 61570-260-10	**Synercid** IV 500 mg	150 mg quinupristin and 350 mg dalfoptistin	10 vials
NDC 61570-261-10	**Synercid** IV 600 mg	180 mg quinupristin and 420 mg dalfoptistin	10 vials

CLINICAL STUDIES
NON-COMPARATIVE TRIALS
In the non-comparative trials, patients often presented with multiple co-morbidities and/or physiologic impairments, and may have been intolerant to or failed other antibacterial therapies.
Vancomycin-Resistant *Enterococcus Faecium*
Results are available from four non-comparative studies of **Synercid** (7.5 mg/kg q8h) for the treatment of vancomycin-resistant *Enterococcus faecium* (VREF) (N=1222). Three of these studies were prospective, the fourth consisted of a collection of individual emergency-use requests.
Of the 1222 patients, 27% did not have a specific site of infection identified, but presented with pure growth of VREF in two or more blood cultures. Ninety percent (90%) of these patients had clearance of their VREF bacteremia within the first 48 to 72 hours of therapy.
Because of the emergency use nature of the VREF trials and the variability in data collection in these severely ill patients, the percentage of patients found to be evaluable was 24.4%. The overall efficacy rate (defined as clinical success and eradication of the initial pathogen) in the evaluable patients (n=298) was 52.3%. The most common sites of infection included intra-abdominal, skin and skin structure, and the urinary tract. In these subgroups, the efficacy rates for the evaluable patients having the most complete documentation were 46.3% (n=67), 66.7% (n=15), and 73.9% (n=23), respectively.
The most common adverse reactions considered related to **Synercid** use were myalgias and arthralgias. (See **ADVERSE REACTIONS**.) All-cause mortality in the 4 studies ranged from 49.5% to 54.0%.

COMPARATIVE TRIALS

Complicated Skin and Skin Structure Infections

Two randomized, open-label, controlled clinical trials of **Synercid** (7.5 mg/kg q12h intravenously [iv]) in the treatment of complicated skin and skin structure infections were performed. The comparator drug was oxacillin (2g q6h iv) in the first study (JRV 304) and cefazolin (1g q8h iv) in the second study (JRV 305); however, in both studies vancomycin (1g q12h iv) could be substituted for the specified comparator if the causative pathogen was suspected or confirmed methicillin-resistant staphylococcus or if the patient was allergic to penicillins, cephalosporins or carbapenems. Study JRV 304 enrolled 450 patients (n = 229 **Synercid**; n= 221 Comparator) and Study JRV 305 enrolled 443 patients (n = 221 **Synercid**; n = 222 Comparator).

In the first study, 105 patients (45.9%) and 106 patients (48.0%) in the **Synercid** and Comparator arms, respectively, were found to be clinically evaluable. For the second study, these values were 113 (51.1%) and 120 (54.1%) patients in the **Synercid** and Comparator arms, respectively. Patients were found not to be clinically evaluable for reasons such as: wrong diagnosis, lower extremity infection in patients with diabetes or peripheral vascular disease since these infections were assumed to include aerobic gram-negative and anaerobic organisms, no specimen for culture obtained, insufficient therapy, no test of cure assessment, etc.

For the patients found to be clinically evaluable, in Study JRV 304 the success rate was 49.5% in the **Synercid** arm and 51.9% in the Comparator arm. In Study JRV 305, the success rates were 66.4% and 64.2% in the **Synercid** and Comparator arms, respectively.

The following table shows the clinical success rate (combined results from two clinical trials) in the clinically evaluable population. Due to the small numbers of patients in the subsets, statistical conclusions could not be reached.

	Cured or Improved			
Infection Type	**Synercid**		**Comparator**	
	(n/N)	(%)	(n/N)	(%)
Erysipelas (cellulitis)	52/82	(63.4)	43/77	(55.8)
Post-operative infections	14/38	(36.8)	24/42	(57.1)
Traumatic wound infection	33/55	(60.0)	33/55	(60.0)

SAFETY

Discontinuations of therapy because of adverse reactions which were probably or possibly due to drug therapy occurred more than four times as often in the **Synercid** group than in the comparator group. Approximately half of the discontinuations in the **Synercid** arm were due to venous adverse events. (See **ADVERSE REACTIONS: Clinical Reactions: Skin and Skin Structure Studies**.)

Keep out of the reach of children.

REFERENCES

1. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* - Fourth Edition; Approved Standard. NCCLS Document M7-A4 (ISBN 1-56238-309-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1997.2. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Sixth Edition; Approved Standard. NCCLS document M2-A6 (ISBN 1-56238-308-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 1997.

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