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

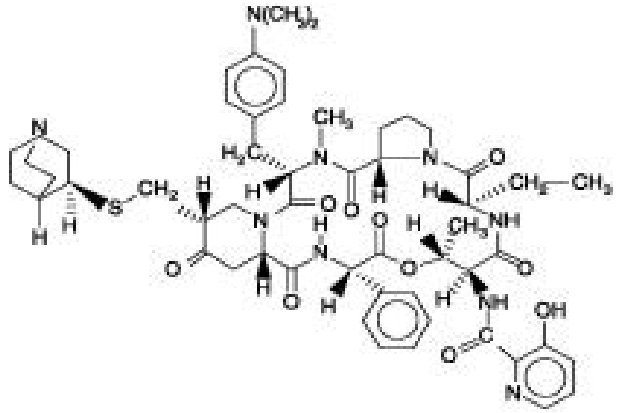
To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Synercid** and other antibacterial drugs, **Synercid** should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

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).

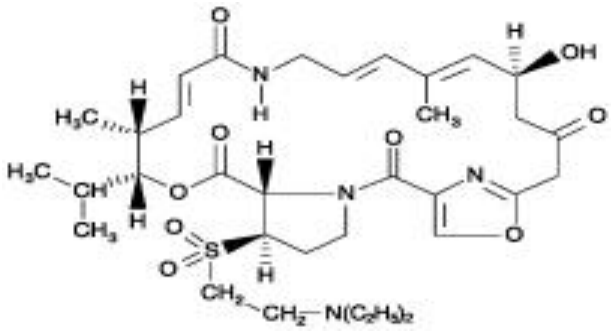
Quinupristin is a white to very slightly yellow, hygroscopic powder. It is a combination of three peptide macrolactones. The main component of quinupristin (> 88.0%) has the following chemical name: N-[(6*R*,9*S*,10*R*,13*S*,15*aS*,18*R*,22*S*,24*aS*)-22-[*p*-(dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-[[(3*S*)-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 Table 1:

Table 1: 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] (mcg/mL)	AUC[3] (mcg.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 total protein binding of quinupristin is higher than that of dalfopristin. **Synercid** does not alter the *in vitro* binding of warfarin to proteins in human serum.

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 mcg/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 ≥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.

Mechanism of Action

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

Resistance

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

Interaction with other Antibacterials

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), β-lactams (cefepime, ampicillin, and amoxicillin), glycopeptides (vancomycin), quinolones (ciprofloxacin), tetracyclines (doxycycline) and also chloramphenicol against enterococci and staphylococci did not show antagonism.

Antimicrobial Activity

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

Gram-positive bacteria
Staphylococcus aureus (methicillin-*susceptible* isolates only)
Streptococcus pyogenes

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

At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the *susceptible* breakpoint for quinupristin and dalfopristin (**Synercid**) against isolates of similar genus or organism group. However, the efficacy of **Synercid** in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria
Corynebacterium jeikeium
Staphylococcus aureus (methicillin-*resistant* isolates)
Staphylococcus epidermidis (including methicillin-*resistant* isolates)
Streptococcus agalactiae

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative reports of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure[1] (broth and/or agar). MIC values should be determined using quinupristin/dalfopristin in a 30:70 ratio. The MIC values should be interpreted according to the criteria in Table 2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using standard test methods[1]. This procedure uses paper disks impregnated with 15 mcg quinupristin/dalfopristin in a ratio of 30:70 to test the susceptibility of bacteria to quinupristin/dalfopristin. The disk diffusion breakpoints are provided in Table 2.

Table 2: Susceptibility Interpretive Criteria for Quinupristin/Dalfopristin

Pathogen and Isolate Source	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
Staphylococcus aureus	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15
Streptococcus pyogenes[a,b]	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15

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

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

A report of *Susceptible (S)* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate (I)* 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 that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant (R)* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and techniques of the individuals performing the test[1]. Standard quinupristin/dalfopristin powder in a 30:70 ratio

should provide the following range of MIC values noted in Table 3[1]. For the diffusion technique using the 15 mcg quinupristin/dalfopristin disk in a ratio of 30:70, the criteria in Table 3 should be achieved.

Table 3: Acceptable Quality Control Ranges for Quinupristin/Dalfopristin Susceptibility

Quality Control Organism	Minimum Inhibitory Concentration Range (MIC in mcg/mL)	Disk Diffusion Zone Diameter (mm)
Staphylococcus aureus ATCC 29213	0.25-1	
Staphylococcus aureus ATCC 25923		21-28
Streptococcus pneumoniae ATCC 49619[a]	0.25-1	19-24

[a] *Streptococcus pneumoniae* is used when testing *Streptococcus pyogenes*.

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

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Synercid** and other antibacterial drugs, **Synercid** should be used only to treat or prevent infections that are proven or strongly suspected to be caused by *susceptible* bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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

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 4: 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

Prescribing **Synercid** in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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 ADVERSE REACTIONS: 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.

Patients should be counseled that antibacterial drugs including **Synercid** should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When **Synercid** is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by **Synercid** or other antibacterial drugs in the future.

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), β-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: 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:

Table 5: Percent (%) 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:

Table 6: Adverse Reactions with an Incidence of ≥1% and Possibly or Probably Related to Synercid Administration

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:

Table 7: Drug Related Events Most Frequently Leading to Discontinuation of Therapy

	% 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:

Table 8: The Most Frequently Reported Venous and Non-Venous Adverse Reactions Possibly or Probably Related to Study Drug

	% 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

Table 9 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).

Table 9: Laboratory Events

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 are presented in Table 10:

Table 10: The Most Common Events Probably or Possibly Related to Therapy

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.) 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. The recommended dosage for the treatment of complicated skin and skin structure infections is 7.5 mg/kg q12h. The minimum recommended treatment duration for complicated skin and skin structure infections is seven days.

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: The recommended dose of **Synercid** for pediatric patients (12 to < 18 years of age) is 7.5 mg/kg q12h. No dosing recommendations are available in pediatric patients less than 12 years of age. (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.
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:

Table 11: 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 8°C (36 to 46°F).

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 8°C (36 to 46°F). 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.

NDC 61570-260-10	**Synercid** IV 500 mg	150 mg quinupristin and 350 mg dalfopristin	10 vials

CLINICAL STUDIES

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.

Table 12 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.

Table 12: The Clinical Success Rate in the Clinically Evaluable Population

	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. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility testing. CLSI document M100-S26. CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA 19807, 2016.

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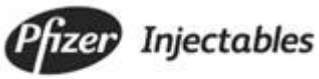

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