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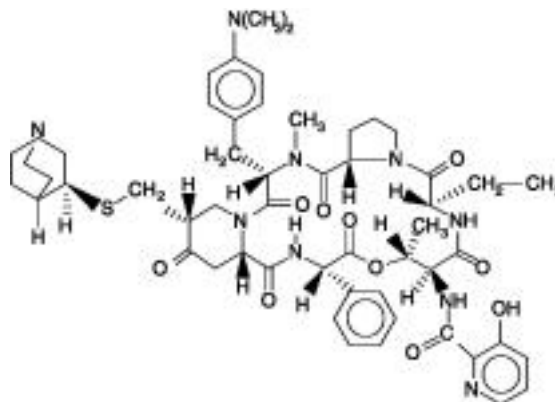
## Synercid<sup>®</sup> I.V. (quinupristin and dalfopristin for injection)

### DESCRIPTION

**Synercid<sup>®</sup>** (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-ethyl-docosahydro-10,23-dimethyl-5,8,12,15,17,21,24-hepta-oxo-13-phenyl-18-[[[(3*S*)-3-quinuclidinylthio] methyl]-12*H*-pyrido[2,1-*f*]pyrrolo-[2,1-*l*][1,4,7,10,13,16] oxapentaazacyclonadecin-9-yl]-3-hydroxypicolinamide.

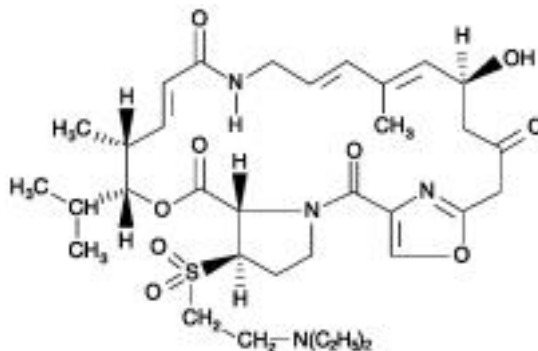
The main component of quinupristin has an empirical formula of C<sub>53</sub>H<sub>67</sub>N<sub>9</sub>O<sub>10</sub>S, a molecular weight of 1022.24 and the following structural formula:



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*,26*aS*)-26-[[2-(diethylamino)ethyl]sulfonyl]-8,9,14,15,24,25,26,26*a*-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<sub>34</sub>H<sub>50</sub>N<sub>4</sub>O<sub>9</sub>S, a molecular weight of 690.85 and the following structural formula:

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## 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 ( $\pm$ SD<sup>1</sup>) (dose = 7.5 mg/kg q8h; n=10)

	C <sub>max</sub> <sup>2</sup> ( $\mu$ g/mL)	AUC <sup>3</sup> ( $\mu$ g.h/mL)	t <sub>1/2</sub> <sup>4</sup> (hr)
Quinupristin and metabolites	3.20 $\pm$ 0.67	7.20 $\pm$ 1.24	3.07 $\pm$ 0.51
Dalfopristin and metabolite	7.96 $\pm$ 1.30	10.57 $\pm$ 2.24	1.04 $\pm$ 0.20

<sup>1</sup> SD= Standard Deviation

<sup>2</sup> C<sub>max</sub> = Maximum drug plasma concentration

<sup>3</sup> AUC = Area under the drug plasma concentration-time curve

<sup>4</sup> t<sub>1/2</sub> = 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.

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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 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

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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  $\beta$ -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.

### **Mechanism of 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),  $\beta$ -lactams (cefepime, ampicillin, and amoxicillin), glycopeptides (vancomycin), quinolones (ciprofloxacin), tetracyclines (doxycycline) and also chloramphenicol against enterococci and staphylococci did not show antagonism.

**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**.

The combination of quinupristin and dalfopristin (**Synercid**) exhibits *in vitro* minimum inhibitory concentrations (MIC's) of  $\leq 1.0$   $\mu\text{g/mL}$  against most ( $\geq 90\%$ ) isolates of the following microorganisms; however, the safety and effectiveness of **Synercid** in treating clinical infections due to these bacteria have 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*

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## SUSCEPTIBILITY TEST METHODS

### 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. Standardized procedures are based on a dilution<sup>1</sup> 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 are interpreted according to the following criteria:

#### For Susceptibility Testing of *Staphylococcus* spp. and *Streptococcus* spp. (excluding *Streptococcus pneumoniae*)<sup>a</sup>

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

<sup>a</sup>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 bacterium 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 bacteria 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 strain:

Microorganisms (ATCC <sup>®</sup> #)	MIC (µg/mL)
<i>Staphylococcus aureus</i> (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<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg

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quinupristin/dalfopristin in a ratio of 30:70 (**Synercid**) to test the susceptibility of bacteria to quinupristin/dalfopristin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg quinupristin/dalfopristin disk are interpreted according to the following criteria:

**For Susceptibility Testing of Staphylococcus spp. and Streptococcus spp. (excluding Streptococcus pneumoniae)<sup>b</sup>**

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

<sup>b</sup>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<sub>2</sub>.

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 bacteria 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 indicated quality control strain.

Microorganism (ATCC® #)	Zone Diameter Range (mm)
<i>Staphylococcus aureus</i> (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.

**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).

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## 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.

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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 [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.

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### 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),  $\beta$ -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**.

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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  $\geq 65$  years of age, of which 145 were  $\geq 75$  years of age. In the phase 3 non-comparative trials, 29% of patients (n=346) were  $\geq 65$  years of age, of which 112 were  $\geq 75$  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:

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**% of patients discontinuing therapy by reaction type**

<b>Type</b>	<b>Synercid</b>	<b>Comparator</b>
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  $\geq 1\%$  and possibly or probably related to **Synercid** administration include:

<b>Adverse Reactions</b>	<b>% of patients with adverse reactions</b>	
	<b>Synercid</b>	<b>Comparator</b>
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

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**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:

<b>Type</b>	<b>% of patients discontinuing therapy by reaction type</b>	
	<b>Synercid</b>	<b>Comparator</b>
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:

	<b>% of patients with adverse reactions</b>	
	<b>Synercid</b>	<b>Comparator</b>
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).

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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 <sub>2</sub>	> 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 <sup>3</sup>	2 (0.2)	2 (0.2)
	< 50,000/mm <sup>3</sup>	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

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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.

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## 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:

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### 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
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## 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.

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.

Infection Type	Cured or Improved			
	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.**

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## REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* – 8<sup>th</sup> Edition; Approved Standard. NCCLS Document M07-A8. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 2009.
2. CLSI. *Performance Standards for Antimicrobial Disk Susceptibility Tests* – 10<sup>th</sup> Edition; Approved Standard. CLSI document M02-A10 2009.

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