Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Synercid 180/420 mg Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 180 mg quinupristin and 420 mg dalfopristin as the mesilate salts.
For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
A slightly yellow to yellow compact mass.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Synercid should only be used when there is documentation to the effect that no other antibacterial agents are active against the causative organism(s) and when there is no other drug which is suitable for treatment of the infection in the individual patient.

Synercid is indicated for the treatment of the three following infections when known to be caused by susceptible Gram-positive organisms and when intravenous therapy is appropriate:

- nosocomial pneumonia
- skin and soft tissue infections
- clinically significant infections due to vancomycin resistant E. faecium

(See Sections 4.4 Special Warnings and Special Precautions for Use and 5.1 Pharmacodynamic Properties).

Synercid should be used in combination with an agent(s) active against Gram-negative organisms if a mixed infection is documented or suspected.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Synercid should be administered through a central venous catheter in 5% glucose solution over a 60-minute period (see Section 6.2 Incompatibilities). It is very important that attention is given to the instructions for dilution prior to use (see Section 6.6 Instructions for Use/Handling).

The safety and efficacy of an intravenous infusion duration of less than 60 minutes has not been evaluated in clinical trials; shorter administration periods must not be used.

Following completion of the infusion, the vein should be flushed with 5% glucose solution to minimise venous irritation. Flushing with saline or heparin immediately after Synercid administration should be avoided. Synercid is incompatible with saline solutions.

Administration of Synercid through a peripheral vein is associated with local adverse effects such as thrombophlebitis. Therefore, Synercid should be administered through a central venous catheter. However, in case of emergency, the first dose of Synercid may be initiated by peripheral intravenous infusion until a central catheter is in place.

Recommended Dosage Schedule			
Indication	Dose (mg/kg)	Frequency	Duration
Skin and skin structure infections	7.5	8 hourly	7 days
Nosocomial pneumonia*	7.5	8 hourly	10 days
Infections caused by vancomycin-resistant *Enterococcus faecium*	7.5	8 hourly	**
* Experience with Synercid in patients with nosocomial pneumonia according to the restricted indication (see Section 4.1) is limited. Therefore, cautious use of Synercid in such patients is indicated together with all necessary considerations for combination therapy with other effective anti-bacterial agents especially in polymicrobial infections.			
** Duration of therapy depends on the site of infection			

Special Populations

Elderly: No dosage adjustment is required for use in the elderly.

Renal Insufficiency: No dosage adjustment of Synercid is required for use in patients with renal impairment and patients undergoing peritoneal dialysis. (See Sections 4.4 Special Warnings and Special Precautions for use and 5.2 Pharmacokinetic Properties).
No investigation has been conducted in anuric and/or haemodialysis patients.

Hepatic Insufficiency: For patients with mild hepatic insufficiency no dose adjustment is necessary.
For patients with moderate hepatic insufficiency (Child-Pugh B score) a dose reduction to 5mg/kg should be considered; however this recommendation is based on limited data and may not be optimal. The efficacy of this dose adjustment has not been clinically evaluated. Therefore, clinical response to treatment should be closely monitored in these patients.
Synercid is contraindicated in patients with severe hepatic insufficiency, since it has not been studied in this population (see Sections 4.3 Contraindications, 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetic Properties). In addition, it is contra-indicated in patients who have significantly raised bilirubin levels (i.e. >3 upper normal limit).

Obese Patients: No dosage adjustment is required for use in obese patients.

Paediatric Patients: Although paediatric patients have been treated with Synercid, its safety and efficacy have not been established for patients of less than 18 years. Therefore there are insufficient data on which to base a dose recommendation.

4.3 Contraindications

Synercid is contraindicated in patients with known hypersensitivity to the active substances quinupristin, dalfopristin or other streptogramins (e.g. pristinamycin and virginiamycin) or to any of the excipients.

Synercid is contraindicated in patients with severe hepatic insufficiency and in patients who have significantly raised bilirubin levels (i.e. > 3 time's upper normal limit) (see Sections 4.2 Posology and Method of Administration and 4.4 Special Warnings and Special Precautions for Use).

Co administration of Synercid with ergot alkaloid derivatives (e.g. ergotamine, dihydroergotamine) and with drugs which are metabolised by cytochrome P450 3A4 enzyme system and which may prolong the QTc interval (e.g. terfenadine, astemizole, cisapride, disopyramide, quinidine and lignocaine) should be avoided.

Co administration of Synercid with any drug(s) metabolised by CYP 3A4 for which the therapeutic window is narrow

should be avoided unless assays of drug levels and/or close clinical monitoring are possible (see Sections 4.4 Special Warnings and Special Precautions for Use and 4.5 Interactions).

Administration of Synercid other than by slow infusion is contraindicated (see Section 4.2 Posology and Method of Administration).

4.4 Special warnings and precautions for use

Some in vitro studies have indicated that the activity of Synercid against *S. aureus* which are constitutively resistant to macrolides, lincosamides and type B streptogramins (MLSB-C resistance) is reduced compared with that against isolates which do not possess this mechanism of resistance. In general, the majority of methicillin-resistant *S. aureus* (MRSA) express MLSB-C.

In the absence of ECG monitoring during clinical trials, Synercid should be used with caution in patients at risk of cardiac arrhythmias (e.g. congenital QT-syndrome, cardiac hypertrophy, dilated cardiomyopathy, hypokalaemia,, bradycardia, hypomagnesiaemia and concurrent administration of QT interval-prolonging agents) (see Section 5.3 Preclinical Safety Data).

Synercid is an inhibitor of CYP3A4. Caution is recommended whenever Synercid is to be co administered with any drug which is metabolised by this route. The addition of any other drugs which inhibit CYP3A4 should be avoided in these circumstances (see Sections 4.3 Contraindications, 4.5 Interactions with Other Medicaments and Other Forms of Interaction and 5.2 Pharmacokinetics).

Episodes of arthralgia and myalgia, some severe, have been reported in patients treated with Synercid. Treatment discontinuation has been followed by symptom resolution. The aetiology of these myalgias and arthralgias is under investigation.

For hepatic insufficiency patients please refer to section 4.2 Posology and Method of Administration and 5.2 Pharmacokinetic properties.

In some patients, isolated hyperbilirubinaemia (primarily conjugated) can occur during treatment, possibly resulting from competition between Synercid and bilirubin for excretion.

In addition, plasma concentrations of quinupristin metabolites are increased by more than five-fold when total bilirubin exceeds three times the upper limit of normal. It is not known what effect, if any, these increases in exposure to metabolites have on the safety and efficacy of Synercid.

An isolated moderate rise in bilirubin (< 3 time’s upper normal limit) is not in itself an indication for interrupting treatment; rather, the decision should be made after consideration of the patient’s overall condition.

In long term therapy, periodic laboratory evaluation of haematological, renal and hepatic function tests should be considered.

Following completion of the infusion, the vein should be flushed with 5% glucose solution to minimise venous irritation. Flushing with saline or heparin immediately after Synercid administration should be avoided.

As with other antimicrobials, use of Synercid may result in overgrowth of non-susceptible micro-organisms (e.g. *E. faecalis* and Gram-negative pathogens). Should superinfection occur during therapy, appropriate measures should be taken.

Pseudomembranous colitis has been reported in association with the use of broad spectrum antibiotics including Synercid, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of Synercid. In this situation adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

Serious and occasionally fatal hypersensitivity (anaphylactic or anaphylactoid) reactions, some following the first dose,

have been reported in patients receiving Synercid therapy. In such cases, therapy with Synercid should be discontinued immediately, and suitable treatment (e.g. treatment for shock) should be initiated.

As Synercid belongs to macrolide-lincosamid-streptogramin antibiotics, the use of this antibiotic constitutes a potential risk for aggravation of symptoms in patients with myasthenia gravis.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro drug interaction studies have demonstrated that the cytochrome P450 3A4 isoenzyme is significantly inhibited by Synercid and that the CYP 3A4 metabolism of cyclosporin A, midazolam, nifedipine and terfenadine is inhibited by Synercid.

Concomitant administration of Synercid and cyclosporin (oral single dose), nifedipine (oral repeated dose) and midazolam (intravenous bolus dose) in healthy volunteers led to elevated plasma levels of these drugs: Cmax increased by 25, 18, and 14% (median values) respectively and AUC increased by 63, 44 and 38% (median values) respectively. Thus it is recommended to monitor blood cyclosporin levels at the beginning of concomitant treatment with Synercid. Close clinical monitoring is recommended when Synercid is given concomitantly with nifedipine or midazolam.

Rifampicin is a potent inducer of CYP450. Synercid is an inhibitor of CYP3A4, one of the isoenzymes of CYP450. In a study in healthy volunteers no changes in the pharmacokinetics of rifampicin, quinupristin or dalfopristin were observed, when rifampacin and Synercid were co-administered. However, rifampacin did increase the AUC of quinupristin's metabolites, leading to an average 43% increase of the AUC of the sum of quinupristin and its active metabolites, possibly through inhibition of their excretion. Liver CYP3A4 activity as measured by erythromycin breath test, was increased when the two drugs were co-administered, suggesting that the inductive effect of rifampacin predominates on the inhibitory effect of Synercid.

Consequently, a close monitoring of bilirubin should be performed regularly in case of co-administration of both products.

Co-administration of Synercid with FK-506 (tacrolimus) resulted in increases in trough levels of this agent by about 15%. In the absence of any other data, it is recommended to monitor tacrolimus blood levels at the beginning of concomitant treatment with Synercid.

Thus, it is reasonable to expect that the concomitant administration of Synercid and other drugs primarily metabolised by the CYP 3A4 enzyme system will result in increased plasma levels of these other agents with a potential for adverse events as a consequence (see Sections 4.3 Contraindications, 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetic Properties).

At a concentration of 10 times maximal plasma concentration in man, Synercid does not significantly inhibit cytochrome P450 1A2, 2A6, 2C9, 2C19, 2D6 or 2E1 in vitro. The clinical relevance of these in vitro data has not been assessed in vivo.

In the absence of ECG monitoring during clinical trials, caution should be exercised when Synercid is given concomitantly with drugs known to prolong QT interval, class Ia and III antiarrhythmic agents, neuroleptics, antidepressants, some antibiotics (antimalarial agents, fluoroquinolones, azol-antimycotics, and macrolides), some non sedating antihistamines.

A slight increase in transaminase level has been reported when Synercid was given concomitantly with acetaminophen or with other drugs known to decrease intracellular glutathione levels.

4.6 Pregnancy and lactation

Pregnancy

No studies have been performed in pregnant women. Synercid should only be used in pregnancy if the physician considers that the benefits outweigh the potential risk (see Section 5.3 Preclinical Safety Data).

Lactation

Synercid passes into rat's milk. It is not known whether Synercid is excreted in human breast milk. Consequently, lactating women should be advised not to breast feed during Synercid treatment.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or headache, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The safety of Synercid has been evaluated in 1099 patients enrolled in 5 comparative clinical trials and in 1199 patients in four non-comparative studies. This latter group of patients received Synercid for infections due to Gram-positive bacteria for which no other treatment option was appropriate. The patients in this population were severely ill, with multiple background diseases and physiological impairments.

The following frequency rating has been used:

very common: >1/10;
common: >1/100, <1/10;
uncommon: > 1/1,000, < 1/100;
rare: >1/10,000, <1/1,000;
very rare: < 1/10,000).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE EVENT
Infections and Infestations	Uncommon	Cellulitis, infection, oral candidiasis, pharyngitis, pneumonia, pseduomembraneous colitis, urinary tract infection, vaginitis
Blood and Lymphatic Disorders	Common	Eosinophilia, anaemia, leucopenia, neutropenia
	Very rare	Pancytopenia, severe thrombocytopenia
Immune System Disorders	Uncommon	Allergic and anaphylactic/toid reaction, which may be life-threatening
Metabolism and Nutritional Disorders	Uncommon	Anorexia, gout
	Rare	Hyponatraemia
Psychiatric Disorders	Uncommon	Anxiety, confusion, insomnia
Nervous System Disorders	Common	Headache
	Uncommon	Paresthesia, dizziness, hypertonia, myasthenia

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE EVENT
Cardiac Disorders	Uncommon	Palpitations, tachycardia, arrhythmia
Vascular Disorders	Common	Haemorrhage, thrombophlebitis
	Uncommon	Hypotension, phlebitis, vasodilatation
Respiratory, Thoracic, and Mediastinal Disorders	Uncommon	Dyspnoea, pleural effusion
Gastrointestinal Disorders	Common	Nausea, diarrhoea, vomiting
	Uncommon	Stomatitis, dyspepsia, constipation, pancreatitis, abdominal pain
Hepatobiliary Disorders	Uncommon	Jaundice, hepatitis
Skin and Subcutaneous Tissue Disorders	Common	Rash, pruritus
	Uncommon	Maculopapular rash, sweating, Urticaria
Musculoskeletal and Connective Tissue Disorders	Common	Arthralgia, myalgia (see Section 4.4, Special Warnings and Special Precautions for Use).
	Uncommon	Back pain, leg cramps
Renal and Urinary Disorders	Uncommon	Haematuria
General Disorders and Administration Site Conditions	Common	Asthenia, infusion site reactions including inflammation, oedema and pain (see Section 4.4, Special Warnings and Special Precautions for Use).
	Uncommon	Chest pain, fever, peripheral oedema
Investigations	Common	Increased total and conjugated bilirubin, ALT, AST, GGT, alkaline phosphatase, blood urea nitrogen, lactate dehydrogenase, creatinine phosphokinase, creatinine, increase and decrease in platelets
	Rare	Increase and decrease in potassium

In post marketing, severe falls in platelet count, anaphylactoid reactions and angioedema have been reported very rarely.

4.9 Overdose

No symptomatic cases of overdose with Synercid have been reported. Patients who receive an overdose should be carefully observed and given supportive treatment. Synercid is not removed by peritoneal dialysis (see Section 5.2 Pharmacokinetic Properties). The high molecular weight of both components of Synercid suggests that it is unlikely to be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Macrolides, lincosamides & streptogramins, ATC Code J01FG02.

Microbiology

The streptogramin A (dalfopristin) and B (quinupristin) components of Synercid are presented for medicinal use in a 70:30 ratio. Quinupristin and dalfopristin each possess in vitro bacteriostatic activity against many Gram-positive bacterial species and act synergistically. This synergism provides bactericidal activity against macrolide susceptible staphylococci and streptococci. In addition, the major metabolites of both quinupristin and dalfopristin display synergy with the complementary parent compound in vitro.

The ways in which the A and B streptogramin components interact at the bacterial ribosome to achieve inhibition of bacterial protein synthesis is complex. Binding of A components to the ribosome is followed by separate binding of B molecules. A stable conformational change in the ribosome occurs and protein synthesis is switched off.

There is no cross-resistance between Synercid and β-lactams, aminoglycosides, glycopeptides, quinolones, or tetracyclines as measured by MIC.

Some in vitro studies have indicated that the activity of Synercid against *S. aureus* which are constitutively resistant to macrolides, lincosamides and type B streptogramins (MLSB-C resistance) is reduced compared with that against isolates which do not possess this mechanism of resistance. Against such strains, Synercid shows no bactericidal activity and a moderate post-antibiotic effect. Among MRSA (methicillin-resistant Staphylococcus aureus), the rate of MLSB-C resistant strains is approximately 75-80%; clinical data are limited. Among MSSA (methicillin-susceptible Staphylococcus aureus), the rate of MLSB-C resistant strains is approximately 5-20% in the EU.

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

In general, in vitro combination testing of Synercid with: glycopeptides, β-lactams, quinolones, tetracyclines, and chloramphenicol against enterococci and staphylococci did not show antagonism. Also, in vitro combination testing of Synercid with aminoglycosides did not show antagonism except in one in vitro study in which Synercid antagonised the killing effect of oxacillin and gentamicin against methicillin-susceptible *Staphylococcus aureus* (ATCC 29213) and of ampicillin against *E. faecalis* (ATCC 29292).

A prolonged post-antibiotic effect (PAE) of Synercid was observed with *Staphylococcus aureus* (10 hours) and *Streptococcus pneumoniae* (9.1 hours) in the neutropenic mouse thigh abscess model, confirming in vitro data on *Staphylococcus aureus* and *E. faecium* of 4 to 6 hours under analogous test conditions.

Synercid is not active against *Enterococcus faecalis*.

Breakpoints
The following MIC breakpoints have been approved for testing rapidly growing aerobic micro-organisms including *Streptococcus pneumoniae*:

National Committee for Clinical Laboratory Standards (NCCLS)
Susceptible < 1 mg/L; Intermediate 2 mg/L and Resistant > 4 mg/L

British Society of Antimicrobial Chemotherapy (BSAC)
Susceptible < 2 mg/L; Resistant > 4 mg/L

Comité Français de l'Antibiogramme Société Française de Microbiologie (CA-SFM)
Susceptible < 0.5 mg/L; Resistant > 2 mg/L

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether micro-organisms will be susceptible to Synercid. Where resistance patterns for particular species are known to vary within the European Union this is shown below.

In vitro antibacterial spectrum - Category with European range of resistance where this is known to vary			
Susceptible			
Aerobic Gram-positive micro-organisms:			
*Enterococcus faecium*1	9.5 - 33%	*Streptococcus agalactiae*	
S. aureus erythromycin-susceptible1-3	0 - 0.4%	*Streptococcus pneumoniae*	0 - 0.5%
S. aureus erythromycin resistant2	0 - 5%	*Streptococcus pyogenes*	
Intermediately susceptible			
Aerobic Gram-positive micro-organisms:		Anaerobic micro-organisms:	
Group C streptococci		*Clostridium perfringens*	
Group G streptococci		*Peptostreptococcus spp.*	
Insusceptible (Resistant)			
Aerobic Gram-positive micro-organisms:			
Enterococcus avium		*Enterococcus gallinarum*	
Enterococcus casseliflavus		*Pediococcus spp.*	
Enterococcus durans		*Streptococcus bovis*	
Enterococcus faecalis			
Aerobic Gram-negative micro-organisms:			
Enterobacteriaceae		Gram-negative non fermenters, incl.	
Haemophilus influenzae		*Pseudomonas spp*	
Haemophilus parainfluenzae			
Anaerobic micro-organisms:			
Bacteroides spp.		*Prevotella spp.*	
Other Clostridium spp.		*Veillonella spp.*	
Fusobacterium spp.			
1 Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications. 2 Among MRSA, the rate of MLSB-C resistant strains is approximately 75-80%. Synercid shows no bactericidal activity and a moderate post-antibiotic effect. Clinical Data are limited. 3 Among MSSA, the rate of MLSB-C resistant strains is approximately 5-20% in the EU.			

5.2 Pharmacokinetic properties

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

Pharmacokinetic profiles of quinupristin and dalfopristin in combination with their metabolites were determined using bioassay following multiple 60-minute infusions of Synercid in two groups of healthy young male volunteers. Each group received 7.5 mg/kg intravenously 12 hourly or 8 hourly for a total of 9 and 10 doses, respectively. The pharmacokinetic parameters were comparable with both dosage regimens; those of the 8 hourly regimens are shown in the following table:

Mean steady-state pharmacokinetic parameters of quinupristin, dalfopristin and metabolites (±SD) n = 10			
Dose Regimen	**Cmax1 (µg/mL)**	**AUC2 (µg.h/mL)**	**t½3 (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 Cmax = Maximum drug plasma concentration 2 AUC = Area under the drug plasma concentration-time curve 3 t 1/2 = Half-life			

The clearances of unchanged quinupristin and dalfopristin are similar (0.7 L/h/kg), and the apparent volume of distribution for both products is approximately 1.0 L/kg. The elimination half-lives of quinupristin and dalfopristin are approximately 0.9 and 0.75 hours, respectively.

Quinupristin is bound to both albumin and alpha-1-glycoprotein. The protein binding ranges from 55 to 78% for quinupristin and from 11 to 26% for dalfopristin.

Penetration of unchanged quinupristin and dalfopristin in non-inflammatory 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.

Radiolabelled quinupristin and dalfopristin were shown to penetrate into ex vivo human macrophages with ratios of intracellular to extracellular concentrations of 60:1 for quinupristin and 30:1 for dalfopristin after 1 hour. A slow release from macrophages was complete at 5 hours for both quinupristin and dalfopristin.

Metabolism

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. However, Synercid has been shown to be an inhibitor of the CYP 3A4 isoenzyme.

Concomitant administration of Synercid and cyclosporin (oral single dose), nifedipine (oral repeated dose) and midazolam (intravenous bolus dose) in healthy volunteers led to elevated plasma levels of these drugs: Cmax increased by 25, 18, and 14% (median values) respectively and AUC increased by 63, 44 and 38% (median values) respectively (see Section 4.5 Interactions with Other Medicaments and Other Forms of Interaction).

Elimination

Faecal excretion constitutes the main elimination route for both parent drugs and their metabolites (75-77% 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 faecal elimination.

Elderly / Gender / Obese: Pharmacokinetics of quinupristin and dalfopristin are not modified in elderly patients or with gender. In obese patients, the Cmax and AUC of quinupristin increase about 1.3 fold and the AUC of dalfopristin about 1.4 fold.

Renal insufficiency: In a pharmacokinetic study of Synercid administered as repeated 7.5 mg/kg IV doses to patient volunteers with moderate or severe chronic renal failure, altered renal function did not have any significant influence on the systemic exposure or elimination kinetics of quinupristin and its metabolites and dalfopristin and its metabolite No investigation has been conducted in anuric and/or haemodialysis patients. However, the high molecular weight of both compounds of Synercid suggests that it is unlikely to be removed by haemodialysis.
In patients undergoing CAPD, dialysis clearance of quinupristin, dalfpristin and their metabolites is negligible.

Hepatic insufficiency: In a repeated-dose pharmacokinetic study of Synercid in non-infected patient volunteers with liver insufficiency, due to cirrhosis, exposure to the components of Synercid and metabolites and to the sum of dalfopristin and RP12536 was comparable in Child Pugh A patients and healthy volunteers.
Exposure to quinupristin metabolites was significantly increased by about 1.8 times in Child-Pugh A patients (7.5 mg/kg dose) and 1.7 times in Child-Pugh B patients (5 mg/kg dose), as compared to healthy subjects and may be explained by an impairment of biliary excretion.
The reduced dose of 5 mg/kg in Child-Pugh B patients led to exposure to the sum of quinupristin components comparable with that observed in healthy volunteers having received 7.5 mg/kg, but the exposure to the sum of dalfopristin components appeared approximately 45% lower.

Population pharmacokinetic data indicated that plasma concentrations of quinupristin metabolites are increased by more than five-fold when total bilirubin exceeds three times the upper limit of normal.

Children: Pharmacokinetics of Synercid in paediatric

5.3 Preclinical safety data

In animal toxicity studies, the incidence and severity of systemic and local adverse effects were reversible and not cumulative and varied according to the dose, the concentration and duration of infusion.

Repeated treatment with high doses was associated with dermal changes in monkeys and lower red blood cell count parameters in rats and monkeys.

Histamine release was observed in dogs, monkeys and mice at Synercid doses of 5, 20 and 103 mg/kg, respectively. However, this has not been observed in human healthy volunteers at single doses up to 29.4 mg/kg and multiple doses up to 7.5 mg/kg 8 hourly.

All reproductive toxicity studies in mice and rats (embryofoetal toxicity, fertility and peri/postnatal toxicity) have not been performed with doses which gave any safety margin to human exposure. There was no evidence of teratogenic effects when Synercid was administered to rats and mice. At exposure levels comparable to human therapeutic dose, slight foetal immaturity was observed in rats and mice. In lactating rats, quinupristin was excreted in milk.

QT and QTc prolongation has been observed in the monkey receiving repeated bolus administrations of Synercid at a dose close to the human therapeutic dose which gave much higher systemic exposure than the human therapeutic exposure. No QT or QTc prolongation was observed in monkeys when treated with Synercid in the conditions similar to human use.

Carcinogenesis - Mutagenesis

Long-term carcinogenicity studies in animals have not been conducted with Synercid.

Genetic toxicity studies were performed with Synercid, in bacterial and mammalian tests in vivo and in vitro. The tests used included the bacterial reverse mutation (Ames test), the CHO/HGPRT gene mutation test, the in vitro unscheduled DNA synthesis test in rat hepatocytes, the chromosome aberration test in CHO-K1 cells and the in vivo mouse micronucleus test in bone marrow.

No evidence for in vitro mutagenic activity and no induction of DNA repair or in vivo clastogenic effect of Synercid, dalfopristin or quinupristin were detected with these tests.

Synercid was negative in the in vitro chromosome aberration test in CHO-K1 cells. When tested individually, a positive response was observed with dalfopristin at highly cytotoxic concentrations. A negative response was observed with quinupristin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methanesulfonic acid, sodium hydroxide.

6.2 Incompatibilities

SYNERCID SHOULD NOT BE DILUTED WITH SALINE SOLUTIONS AS IT IS NOT COMPATIBLE WITH SODIUM CHLORIDE.

Synercid must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf Life

The shelf life of unopened vials is 3 years.
Reconstituted vials should be further diluted within 30 minutes.
Chemical and physical in-use stability of the diluted infusion solution has been demonstrated for 5 hours at 25ºC.
From a microbiological point of view, the diluted infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Before Reconstitution: Store in a refrigerator (2 - 8°C).
Reconstituted and Infusion Solutions: Do not freeze.

6.5 Nature and contents of container

10mL single dose vial (type I glass) with a grey elastomeric stopper and an aluminium seal with a dark red flip-off cap.

Cartons contain one 600mg sterile single-dose vial.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Vials are for single use, any unused solution should be discarded.

Preparation and administration of solution: As Synercid contains no antibacterial preservative, it should be reconstituted under strict aseptic conditions.

1. Reconstitute the single dose vial by slowly adding 6 mL of 5% glucose solution or sterilise water for injections.

2. Gently swirl the vial by manual rotation without shaking to ensure dissolution of contents while limiting foam formation. This may take at least two minutes.

3. Allow the solution to sit for at least two minutes until all the foam has disappeared. The resulting solution should be clear. As for other parenteral drug products, inspect visually for particulate matter prior to dilution and administration and discard any solution containing precipitates. Vials reconstituted in this manner will give a solution of 100 mg/mL. The quantity of solution to be withdrawn should be adjusted to the patient's weight to obtain a dose of 7.5 mg/kg. The reconstituted vial contents should be further diluted within 30 minutes.

4. For a central venous administration, Synercid solution should be added to 100 mL of 5% glucose solution. For

a peripheral venous administration, Synercid solution should be added to 250 mL of 5% glucose solution (see Section 4.2 Posology and Method of Administration).

5. The desired dose should be administered by intravenous infusion over 60 minutes.

Incompatibilities: Synercid should not be mixed with, or physically added to, other drugs except the following for which compatibility of Synercid by Y-site injection has been established:

Y-Site Injection Stability of Synercid at 2 mg/mL Concentration	
Aztreonam 20 mg/mL	5% glucose
Ciprofloxacin 1 mg/mL	5% glucose
Fluconazole 2 mg/mL	used as undiluted solution
Haloperidol 0.2 mg/mL	5% glucose
Metoclopramide 5 mg/mL	5% glucose
Morphine hydrochloride 1 mg/mL	5% glucose
Potassium chloride 40 mmol/L	5% glucose

If Synercid is to be given concomitantly with another drug, each drug should be given separately in accordance with its recommended dosage and route of administration.

With intermittent infusion of Synercid and other drugs through a common intravenous line, the line should be flushed before and after Synercid administration with 5% glucose.

7 MARKETING AUTHORISATION HOLDER

Monarch Pharmaceuticals Ireland Limited
Alexandra House
The Sweepstakes
Ballsbridge
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