Synercid® I.V.

IDENTIFICATION OF THE MEDICINAL PRODUCT

NAME OF THE PRODUCT : SYNERCID®

QUALITATIVE AND QUANTITATIVE COMPOSITION
Cartons contains one sterile 500 mg single-dose Synercid® vial.
Active ingredients per one single dose vial :
Quinupristin.....150 mg (as the mesilate salts)
Dalfopristin.....350 mg (as the mesilate salts)

Excipient : sodium hydroxide, nitrogen, water for injections.

PHARMACEUTICAL FORM
Powder for solution for infusion in single dose vial.

PHARMACO-THERAPEUTIC CLASS
General anti-infectives for systemic use (J01). Synercid® belongs to the streptogramins group.

WHEN SHOULD THIS DRUG BE USED (THERAPEUTIC INDICATIONS)
- Synercid® is indicated in the treatment of Gram-positive infections caused by susceptible organisms when intravenous therapy is appropriate, in particular in the treatment of :
  - complicated skin and skin structure infections ;
  - nosocomial pneumonia ;
  - clinically significant infections due to *Enterococcus faecium.*
- Synercid® can also be used for treatment of the above indications in beta-lactam-, quinolone- or glycopeptide-allergic or intolerant patients.
- Synercid® should be used in combination with anti-Gram-negative agents for mixed infections if Gram-negative pathogens are suspected or culture proven.

ATTENTION
WHEN SHOULD THIS DRUG NOT BE USED (CONTRA-INDICATIONS)
- Synercid® is contraindicated in patients with known hypersensitivity to one of the ingredients of Synercid® or other streptogramins (e.g. pristinamycin and virginiamycin).
- Administration of Synercid® other than by slow infusion is contraindicated (see Method of administration section).
- Synercid® is an inhibitor of cytochrome P450 3A4 (CYP 3A4). Co-administration of Synercid® with any drugs primarily metabolised by CYP 3A4 should be avoided :
  - **cyclosporin A, midazolam, nifedipine, tacrolimus** (co-administration will result in increased plasma levels of these agents with a potential for adverse events as a consequence) unless assays of drug levels and/or close clinical monitoring are possible ;
  - **terfenadine, astemizole, cisapride, disopyramide, quinidine and lignocaine** (co-administration may prolong the QTc interval).

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

Episodes of arthralgia and myalgia, some severe, have been reported in patients treated with Synercid®. These may improve with a decrease in dose frequency to 12 hours. Treatment discontinuation has been followed by symptom resolution.

Synercid® should be used with caution in patients with hepatic or renal insufficiency.

In some patients, isolated hyperbilirubinemia (primarily conjugated) can occur during treatment, possibly resulting from competition between Synercid® and bilirubin for excretion. An isolated moderate rise in bilirubin is not in itself an indication for interrupting treatment; rather, the decision should be made after consideration of the patient's overall condition.

INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTIONS
- Synercid® is an inhibitor of CYP 3A4. Coadministration of any drugs primarily metabolised by this route is contraindicated (see Contraindications).
- *In vitro* combination testing of Synercid® with aztreonam, cefotaxime, ciprofloxacin, gentamicin, against Enterobacteriaceae and *Pseudomonas aeruginosa* did not show antagonism.
- *In vitro* combination testing of Synercid® with beta-lactams, glycopeptides, quinolones, tetracyclines, and also chloramphenicol against enterococci and staphylococci did not show antagonism.
- *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).

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.

- Lactation:
  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.

HOW SHOULD THIS DRUG BE USED
METHOD OF ADMINISTRATION
Synercid® is recommended to be administered through a central venous catheter in 5% glucose solution over a 60-minute period. The physician may decide to administer Synercid® by peripheral intravenous infusion.

The safety and efficacy of an intravenous infusion duration of less than 60 minutes have 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 solution immediately after Synercid® administration is not recommended. **Synercid® should not be diluted with saline solutions** as it is not compatible with sodium chloride. (*See section instructions for use/handling and incompatibilities*)

DOSAGE

Recommended Dosage Schedule

Indication	Dose (mg/kg)	Frequency	Duration
Skin and skin structure infections*	7.5	12 hourly*	7 days
Nosocomial pneumonia	7.5	8 hourly	10 days
Infections caused by Vancomycin-resistant *Enterococcus faecium*	7.5	8 hourly	**

* **Except when due to macrolide-resistant *Staphylococcus aureus* when an 8-hourly regimen is recommended. Pending susceptibility test results, any methicillin-resistant *Staphylococcus aureus* (MRSA) should be treated with 8-hourly dosing because of the high likelihood of macrolide resistance).**
** Duration of therapy depends on the site of infection

- **Elderly, patients undergoing peritoneal dialysis, obese patients :** No dosage adjustment required.
- **Hepatic, renal insufficient patients :** Synercid® should be used with caution in such 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.

ACTION TO BE TAKEN IN CASE OF OVERDOSE
No symptomatic cases of overdose with Synercid® have been reported. Patient who received an overdose should be carefully observed and given supportive treatment. Synercid® is not removed by peritoneal dialysis. The high molecular weight of both components of Synercid® suggests that it is unlikely to be removed by haemodialysis.

UNDESIRABLE EFFECTS
Like any active product, this drug may induce, in some patients, undesirable effects to a greater or lesser degree. The most common adverse effects are :
- venous adverse reactions (peripheral administration) : inflammation, pain, oedema, injection site reaction, thrombophlebitis and haemorrhage.
- Non-venous adverse reactions : arthralgia and myalgia (may require dose decrease or discontinuation), nausea, diarrhoea, vomiting, rash, headache, pruritus, pain and asthenia.

- Other adverse reaction have rarely been reported : Oral moniliasis, vaginitis, stomatitis, cellulitis, infection, urinary tract infection, pancreatitis, gout, hepatitis, pharyngitis, pseudomembranous colitis, jaundice, vasodilatation, tachycardia, palpitation, hypotension, pneumonia, dyspnoea, pleural effusion, peripheral oedema, allergic reaction, maculopapular rash, urticaria, sweating, paraesthesia, fever, confusion, back pain, abdominal pain, chest pain, anxiety, insomnia, anorexia, dizziness, myasthenia, hypertonia, legs cramps, haematuria, dyspepsia, constipation and hyponatraemia.

- Laboratory changes :
  - Increases in total and conjugated bilirubin.
  - Have been also observed changes in eosinophils counts, blood urea nitrogin, gamma glutamyl transferase, creatine phosphokinase, lactate deshydrogenase, AST, ALT, haemoglobin, haematocrit, potassium, platelets, white blood cells and neutrophils.
  - Thrombocytopenia and one case of pancytopenia have been observed.

STORAGE
Respect the expiry date indicated on the outer packaging.

SPECIAL PRECAUTIONS FOR STORAGE
- **Before Reconstitution :**
  The unopened vials should be stored under refrigeration at 2 to 8°C.
- **Reconstituted and Infusions Solutions :**
  Synercid® should be reconstituted under strict aseptic conditions and reconstituted vials should be further diluted within 30 minutes and the diluted infusion solution used within 5 hours if stored at room temperature (up to 25°C) or 24 hours if refrigerated (2-8°C). The infusion solution should not be frozen.
  Stability of the diluted infusion solution has been demonstrated for 5 hours at room temperature (up to 25°C) or 54 hours if refrigerated at 4°C.
  From a microbiological point of view, the product 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 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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

Synercid® should not be mixed with, or physically added to, other drugs except the following for which compatibility of Synercid® diluted in a 5% glucose solution by Y-site injection has been established :

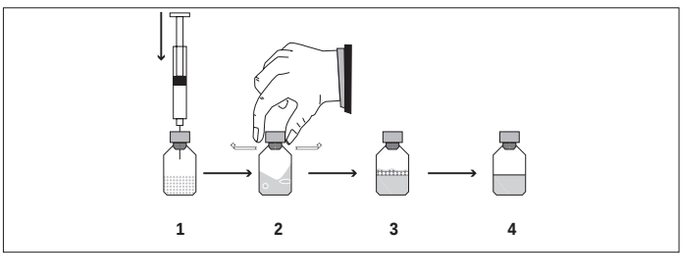
Y-Site Injection stability of Synercid® at 2 mg/mL Concentration
Aztreonam 20 mg/mL
Ciprofloxacin 1 mg/mL
Fluconazole 2 mg/mL used as undiluted solution
Haloperidol 0.2 mg/mL
Metoclopramide 5 mg/mL
Morphine hydrochloride 1 mg/mL
Potassium chloride 40 mmol/L

If Synercid® is to be given concomitantly with other drugs, 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.

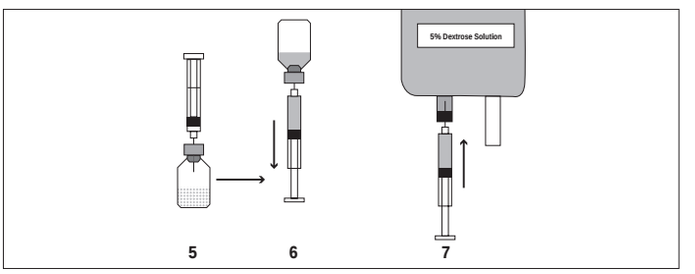
INSTRUCTIONS FOR USE/HANDLING

Vials are for single use ; any unused solution should be discarded.
Preparation and administration of the solution : As Synercid® contains no antibacterial preservative, it should be reconstituted under strict aseptic conditions.
Reconstitution of the single dose vial :
1. Reconstitute the single dose vial by slowly adding 5 mL of 5% glucose solution or sterilised 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.
4. Vials reconstituted in this manner will give a solution of 100 mg/mL. The reconstituted vial contents should be further diluted within 30 minutes.



Preparation of the infusion bags :
5. Penetrate the vial stopper with the syringe needle.
6. Invert the vial and withdraw the required amount of 100 mg/mL solution to obtain 7.5 mg of Synercid® per kg of patient body weight. (To extract the nominal dose of 500 mg, withdraw as much solution as possible from the vial).
7. Inject the syringe contents into 250 mL (for a peripheral line infusion) or 100 mL (for a central line infusion) of 5% glucose solution. Mix the contents by inverting the bag several times.

Administration of the solution :
The desired dose should be administered by intravenous infusion over 60 minutes.



DATE OF REVISION OF PACKAGE INSERT : September 99 401215-01/00

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