CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-747

50-748

PHARMACOLOGY/TOXICOLOGY REVIEW

JAN 27 1998

Roche 520

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA: 50-748 (000) N50-747) VREF

DRUG: Synercid

CATEGORY: Streptogramin antibiotic

SPONSOR: Rhone-Poulenc Rorer Pharmaceuticals
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NUMBER OF VOLUMES: 730 (45 Pharm/Tox)

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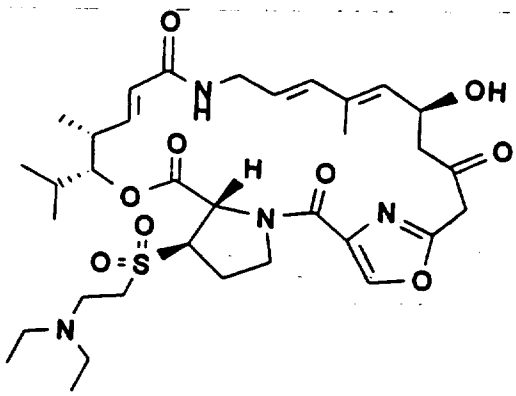
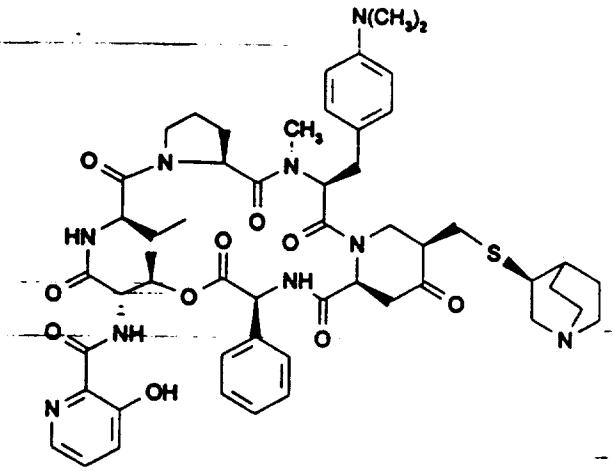
INTRODUCTION/OVERVIEW

Synercid is a mixture of two naturally occurring pristinamycins which are produced by the fermentation of *Streptomyces pristinaespiralis*. Synercid is also known by the alphanumeric code number RP59500. The two components of Synercid are quinupristin (RP 57669) 30% w/w, and dalfopristin (RP 54476) 70% w/w.

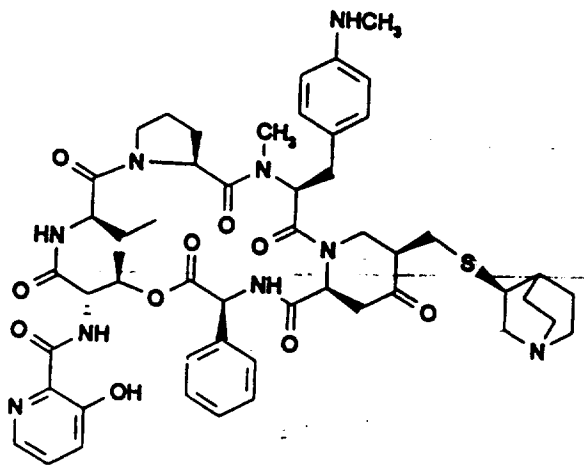
Quinupristin is a combination of three peptide macrolactones (RP 68888, RP 60844, and RP 67648). The chemical structure of dalfopristin and the three components of quinupristin are as follows:



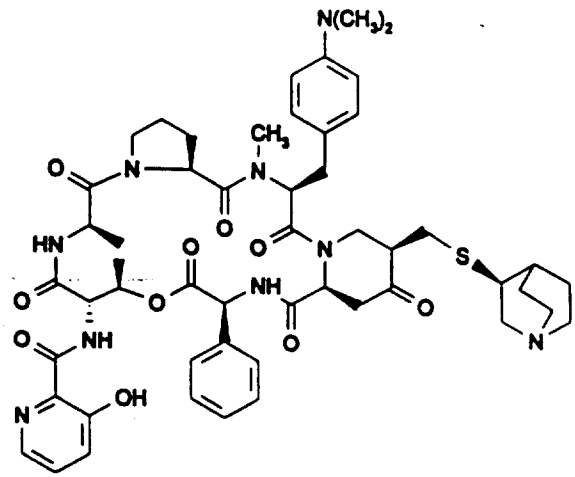
RP 54476



RP 68888



RP 60844



RP 67648

Synercid is active against Gram-positive bacteria. This new drug application seeks approval of Synercid for use in the treatment of [redacted] and complicated skin and skin structure infections. Another NDA (50-747) has been submitted, seeking approval of Synercid for use in the treatment of infections due to Vancomycin-resistant *Enterococcus faecium*.

Synercid is intended to be administered as an intravenous infusion in 5% dextrose solution, at a dose of 7.5 mg/kg of body weight, with the dose to be repeated at intervals of eight or twelve hours.

The sponsor, at the request of the FDA, submitted duplicate INDs for Synercid. The original IND was [redacted] a secondary IND ([redacted] was a Subpart E submission for use in the treatment of infections due to Vancomycin-resistant *Enterococcus faecium*.

NOTE: The sponsors' table of contents for NDA 50-748 contains a minor mistake. Section 5.6.2.4.3 (Volume 1, Page 36) is incorrectly titled "Chromosomal Aberrations in Chinese Hamster Ovary Cells". This section actually contains reports of Unscheduled DNA Synthesis studies.

This NDA consisted of 122 toxicology study reports (Reports 5.18-5.130.I), 19 pharmacology study reports (Reports 5.1-5.17.B), and 47 pharmacokinetic study reports (Reports 5.131-5.177). Every study report was evaluated during the review of this NDA. The information presented in this review has been extracted from the reports of the pivotal preclinical studies in the NDA submission. Additional details on the experimental designs and methodologies can be found in the Pharmacology/Toxicology reviews of the original IND and amendments.

LIST OF STUDIES REVIEWED

Document Number	Title
5.1.	Behavioural and electroencephalographic effects in small rodents of RP 57669 and RP 54476. [redacted] 30 NOV 95
5.2.	Behavioural and electroencephalographic effects of RP 59500 (RP 57669/RP 54476) in small rodents. [redacted] 30 NOV 90
5.3.	Cardiovascular and autonomic nervous system effects of RP 54476 and RP 57669, water soluble derivatives of pristinamycine in anesthetized monkeys. [redacted] 16 MAY 89
5.4.	Cardiovascular (rat, dog, monkey), respiratory (dog, monkey) and autonomic nervous systems (monkey) effects of RP 59500, an injectable hemisynthetic streptogramin. [redacted] 16 MAR 90
5.5.	Effects on blood pressure and heart rate of RP 54476 and RP 57669, water soluble derivatives of pristinamycine, in awake normotensive rats. [redacted] 16 MAY 89
5.6.	Cardiovascular effects of RP 54476 and RP 57669, water soluble derivatives of pristinamycine, in anesthetized dogs. [redacted] 16 MAY 89
5.7.	RP 59500 (RP 57669/RP 54476): *in vitro* transmembrane electrophysiological effects in guinea-pig Purkinje fibers. [redacted] RPR/RD/CRVA/BIOL 598, 13 DEC 94
5.8.	RP 59500: Blood concentrations of its two components and a metabolite and effects on cardiovascular system, histamine plasma levels and hematocrit in anesthetized dogs. [redacted] RPR/RD/CRVA/BIOL 228, 03 JUL 91
5.9.	RP 59500: Blood concentrations of its two components and of a metabolite and effects on cardiovascular system, histamine plasma levels and hematocrit in anesthetized pigs. [redacted] RPR/RD/CRVA/BIOL 229, 3 AUG 93
5.10.	RP 59500 (RP 57669/RP 54476) - *In vitro* receptor binding profile. [redacted] 9900-[redacted] 15 JUN 95

5.11.	RP 57669/RP 54476 - Effects on intestinal transit in rats after intravenous administration. RPR/RD/DISC/BIOL/CRVA 746, 13 OCT 95
5.12.	RP 57669/RP 54476 - Effects on spontaneous gastric acid secretion in rats after intravenous administration. RPR/RD/DISC/BIOL/CRVA 747, 13 OCT 95
5.13.	RP 57669/RP 54476: Effects on bile secretion in the anesthetized rat, after intravenous administration. RPR/RD/DISC/BIOL/CRVA 753, 20 OCT 95
5.14.	Effect of intravenously administered RP 59500 on diuresis in rats. 5 APR 90
5.15.	RP 57669/RP 54476 - Effects by the intravenous route on diuresis in conscious rats. RPR/RD/DISC/BIOL/CRVA 661, 15 JUN 95
5.16.	RP 59500 (RP 57669/RP 54476) - Effects on bleeding time in rats after intravenous administration. RPR/RD/DISC/BIOL/CRVA 711, 8 SEP 95
5.17.	RP 59500 (RP 57669/RP 54476) - Effects on coagulation times in rats after intravenous administration. RPR/RD/DISC/BIOL/CRVA 742, 8 SEP 95
5.17.A	RP 57669/RP 54476 - Effects on hematocrit and plasma histamine levels in rats after intravenous administration. RPR/RD/DISC/BIOL/CRVA 813, 14 JAN 97
5.17.B	RP 57669/RP 54476 - In vitro effects on eicosanoid production during human whole blood spontaneous coagulation. RPR/RD/DISC/BIOL/CRVA 807, 20 MAY 96

Document Number	Title
5.18.	RP 68888 (RP 57669 A) - Acute toxicity study in the mouse by intravenous route - Exploratory study. 1 OCT 90
5.19.	RP 60844 (RP 57669 B) - Acute toxicity in the mouse by intravenous route - Exploratory study. 30 MAR 90
5.20.	RP 67648 (RP 57669 C) - Acute toxicity in the mouse by intravenous route - Exploratory study. 30 MAR 90

5.21.	RP 57669 - Acute toxicity in the rat by intravenous route. 28 AUG 89
5.22.	RP 57669 - Acute toxicity in the monkey by intravenous route. 4 SEP 89
5.23.	RP 54476 - Acute toxicity in the rat by intravenous route. 5 JUN 89
5.24.	RP 54476 - Acute toxicity in the monkey by intravenous route. 30 OCT 89
5.25.	RP 59500 - Acute intravenous toxicity study in the mouse. 24 AUG 89
5.26.	RP 59500 - Intravenous toxicity in the mouse with B.I.D. and T.I.D. dosing schedules for a single day - Exploratory study. 14 DEC 89
5.27.	RP 59500 - Acute intravenous toxicity study in the rat. 24 AUG 89
5.28.	RP 59500 - Acute intravenous lethality study in the rat - Influence of the rate of injection - Exploratory study. 7 DEC 89
5.29.	RP 59500 - Intravenous toxicity in the rat with B.I.D. and T.I.D. dosing schedules for a single day - Exploratory study. 14 DEC 89
5.30.	RP 59500 - Intravenous (1 hour infusion) acute toxicity study in the rat. 28 MAY 91
5.31.	RP 59500 - Intravenous (1 hour infusion) acute toxicity study in the rat - Pathology report. RPR/RD/CRVA/SM 543, 1 JUL 91
5.32.	RP 59500 - Intravenous (4 hour infusion) acute toxicity study in the rat. 28 MAY 91
5.33.	RP 59500 - Acute intravenous lethality study in the rat: influence of formulation. RPR/RD/CRVA/SM 536, 10 SEP 91
5.34.	RP 59500 - Acute toxicity study in the male rat by intravenous route - Effect of pretreatment with dexchlorpheniramin. RPR/RD/CRVA/SM 586, 24 DEC 91

5.35.	RP 57669/RP 54476 (30/70) - Single-dose intravenous toxicity study in rats (comparison of degraded and non-degraded solutions). RPR/RD/CRVA/SM 95-0279, 23 FEB 96
5.36.	RP 59500 - Preliminary acute toxicity study by intravenous administration to cynomolgus monkeys. 29 AUG 89
5.37.	RP 59500 - Acute toxicity study by intravenous administration to cynomolgus monkeys. 11 OCT 89
5.38.	RP 59500 - Intravenous toxicity in the monkey with B.I.D. dosing schedules for a single day - Exploratory study. 14 DEC 89
5.39.	RP 57669 - One month lethality study in the mouse by intravenous route (Pilot study). 13 SEP 89
5.40.	RP 57669 - Toxicity study by intravenous administration to CD rats for four weeks - Final report. 20 JAN 89
5.41.	RP 57669 - Toxicity study by intravenous administration to CD rats for four weeks. First supplement to LSR report 88/RHS 032/641 - Electron microscopy report. 26 OCT 88
5.42.	RP 57669 and RP 54476 - Toxicity study by intravenous administration to cynomolgus monkeys for four weeks followed by a four week reversibility period - Final report. 6 FEB 89
5.43.	RP 57669 and RP 54476 - Toxicity study by intravenous administration to cynomolgus monkeys for four weeks followed by a four week reversibility period. First supplement to LSR report 88/RHS 022/619 - Electron microscopy report. 23 NOV 88
5.44.	RP 54476 - Toxicity study by intravenous administration to CD rats for four weeks - Final report. 30 JAN 89
5.45.	RP 54476 - Toxicity study by intravenous administration to CD rats for four weeks. First supplement to LSR report 88/RHS033/460 - Electron microscopy report. 25 OCT 88

5.42 / 5.46.	RP 57669 and RP 54476 - Toxicity study by intravenous administration to cynomolgus monkeys for four weeks followed by a four week reversibility period - Final report. [redacted] 6 FEB 89
5.43/ 5.47.	RP 57669 and RP 54476 - Toxicity study by intravenous administration to cynomolgus monkeys for four weeks followed by a four week reversibility period. First supplement to LSR report 88/RHS 022/619 - Electron microscopy report. [redacted] 23 NOV 88
5.48.	RP 59500 - Toxicity study by intravenous administration to CD rats for four weeks followed by a four week reversibility period - Final report. [redacted] 6 APR 89
5.49.	RP 59500 - Toxicity study by intravenous administration to CD rats for four weeks followed by a four week reversibility period - First supplement to LSR report 88/RSH 034/748. Electron microscopy report. [redacted] 25 NOV 88
5.50.	RP 59500 - Toxicity study by intravenous administration to CD rats for thirteen weeks followed by a four-week reversibility period - Final report. [redacted] 23 NOV 90
5.51.	RP 59500 - Toxicity study by intravenous administration to CD rats for thirteen weeks followed by a four-week reversibility period. First supplement to LSR report 89/RHS 043/1086 - Electron microscopy report. [redacted] 26 MAR 90
5.52.	RP 59500 - Intravenous toxicity in the rat with B.I.D. dosing schedule for six days - Exploratory study. [redacted] 15 MAR 90
5.53.	Pilot 14-day toxicity study with RP 57669/RP 54476, 30/70, mesylate (RP 59500) following infusion for 1 hour on 2 or 3 occasions per 24 hours in the unrestrained rat. [redacted] 6 JUN 92
5.54.	Pilot 14-day toxicity study with RP 57669/RP 54476, 30/70, mesylate (RP 59500) following infusion for 1 hour on 3 occasions per 24 hours in the unrestrained rat . [redacted] 31 AUG 95
5.55.	28-day T.I.D. intravenous toxicity study of RP 59500 in the albino rat followed by a 28-day recovery period. [redacted] 28 AUG 91
5.56.	91-day toxicity study with RP 57669/RP 54476, 30/70, mesylate (RP 59500) following infusion for 1 hour on 3 occasions per 24 hours in the unrestrained rat. [redacted] 6 MAY 93

5.57.	91-day toxicity study with RP 59500 (RP 57669/RP 54476, 30/70, mesylate) following infusion for 1 hour on 3 occasions per 24 hours in the unrestrained rat - Pathology report. RPR/RD/CRVA/SM 658, 28 OCT 92
5.58.	RP 57669/RP 54476 (30/70) - a 26-week intravenous toxicity study in sprague-dawley rats. 6 AUG 96
5.59.	RP 59500 - Toxicity study by intravenous administration to cynomolgus monkeys for four weeks followed by a four week reversibility period - Final report. 2 FEB 89
5.60.	RP 59500 - Toxicity study by intravenous administration to cynomolgus monkeys for four weeks followed by a four week reversibility period. First supplement to LSR report 88/RHS 026/749 - Electron microscopy study. 12 DEC 88
5.61.	RP 59500 - Toxicity study by intravenous administration to cynomolgus monkeys for 13 weeks followed by a four week reversibility period - Final report. 30 JAN 91
5.62.	RP 59500 - Intravenous toxicity in the monkey with B.I.D. dosing schedules for five days - Exploratory study. 15 MAR 90
5.63.	7-day intravenous pilot study of RP 59500 (RP 57669/RP 54476, 30/70) in the rhesus monkey. 23 APR 93
5.64.	A 15-day study with test article RP 59500 (RP 57669/RP 54476) administered by intravenous infusion to rhesus monkeys. 1 MAR 93
5.65.	RP 59500 (RP 57669/RP 54476, 30/70, mesylate) - Two-week intravenous study in rhesus monkeys - Pathology report. RPR/RD/CRVA/SM 624, 1 APR 93
5.66.	28-day T.I.D. intravenous toxicity study of RP 59500 in the rhesus monkey followed by a 28-day recovery period. 3 SEP 91
5.67.	A 90-day study with test article RP 57669/RP 54476, 30/70, mesylate administered by intravenous infusion to rhesus monkeys followed by a 1-month recovery period. 23 MAR 94
5.68.	90-day study with test article RP 59500 (RP 57669/RP 54476, 30/70, mesylate) administered by intravenous infusion to the rhesus monkey followed by a 1-month recovery period. RPR/RD/CRVA/SM 701, 24 JAN 94

5.69.	A 90-day study with test article RP 57669/RP 54476, 30/70, mesylate administered by intravenous infusion to rhesus monkeys followed by a 1-month recovery period. 23 MAR 94
5.70.	A 3-month study with test article RP 59500 (RP 57669/RP 54476, 30/70, mesylate) administered by intravenous infusion to the rhesus monkey followed by a 1-month recovery period. RPR/RD/CRVA/SM 93-0112, 22 FEB 94
5.71.	RP 57669/RP 54476 (30/70) - A 28-day T.I.D. intravenous toxicity study in rhesus monkeys (comparison of degraded and non-degraded solutions). 26 JUN 96
5.72.	RP 57669/RP 54476 (30/70) - A 28-day T.I.D. intravenous toxicity study in rhesus monkeys (comparison of degraded and non-degraded solutions) - Pathology report. RPR/RD/CRVA/SM 95-0273, 18 APR 96
5.73.	RP 57669/RP 54476 (30/70) - A 26-week T.I.D intravenous toxicity study in rhesus monkeys. 2 AUG 96
5.74.	RP 57669/RP 54476 - Reproductive function and fertility study in the rat. 14 MAR 94
5.75.	RP 59500 - Preliminary teratology study in the mouse. 20 DEC 91
5.76.	RP 57669/RP 54476 - Teratology study in the mouse. 26 APR 93
5.77.	RP 57669/RP 54476 - Teratology study in the mouse. 13 MAY 93
5.78.	RP 59500 - Preliminary teratology study by the intravenous route in the rat. 4 JAN 90
5.79.	RP 59500 - Teratology study in the rat. 11 JUL 90
5.80.	An intravenous infusion teratology study of RP 59500 in the rat. 14 APR 92
5.81.	RP 59500 - Preliminary teratology study by the intravenous route in the rabbit. 27 FEB 90
5.82.	RP 59500 - Teratology study in the rabbit. 5 OCT 90
5.83.	An intravenous infusion range finding teratology study of RP 59500 in the rabbit. 11 NOV 91

5.84.	RP 57669/RP 54476, 30/70, mesylate intravenous peri and post-natality (segment III) study in rats. RPR/RD/CRVA/SM 92-0270, 11 JAN 94
5.85.	RP 57669 - *In-vitro* mutagenicity: Ames test. 4 OCT 89
5.86.	RP 54476 - *In-vitro* mutagenicity: Ames test. 4 OCT 89
5.87.	RP 59500 - *In-vitro* mutagenicity: Ames test. 4 OCT 89
5.88.	RP 57669/RP 54476 (30/70) - Bacterial reverse mutation test (degraded solutions). RPR/RD/CRVA/SM 95-0291, 5 MAR 96
5.89.	RP 57669 - Hypoxanthine-Guanine Phosphoribosyl Transferase Gene Mutation Test in Chinese Hamster Ovary Cells (CHO-K1). RPR/RD/CRVA/SM 422, 1 OCT 91
5.90.	RP 54476 - CHO/HPRT test. 28 JUN 90
5.91.	RP 59500 - CHO/HPRT test. 10 APR 90
5.92.	RP 5766, Pristinamycin - Chromosome aberration test in Chinese Hamster Ovary Cells (CHO). 3 OCT 89
5.93.	RP 54476A - In vitro mammalian chromosome aberration test in Chinese Hamster Ovary Cells (CHO-K1) (Rat liver S9 metabolic activation). 2 MAY 96
5.94.	RP 54476 - Chromosome aberration test in Chinese Hamster Ovary Cells (CHO). 24 MAR 94
5.95.	RP 59500 - Chromosome aberration test in Chinese Hamster Ovary Cells (CHO). 28 AUG 89
5.96.	RP 57669 - *In-vitro* DNA-repair test in rat hepatocytes in primary culture. 11 SEP 89
5.97.	RP 54476 - In-vitro DNA-repair test in rat hepatocytes in primary culture. 11 SEP 89
5.98.	RP 59500 - In-vitro DNA-repair test in rat hepatocytes in primary culture. 18 DEC 89

5.99.	RP 57669 (Pristinamycin PI) - Bone marrow micronucleus test in the mouse by the intravenous route. 18 JAN 89
5.100.	RP 54476 (Pristinamycin PII) - Bone-marrow micronucleus test in the mouse by the intravenous route. 1 JUN 89
5.101.	RP 59500 - Bone-marrow micronucleus test in the mouse by the intravenous route. 16 OCT 89
5.102.	RP 57669/RP 54476 (30/70) - Local intravenous tolerance in rabbits RPR/RD/DS/CRVA 3405-3408-3472-3512-3588 , 4 JUL 96
5.103.	RP 59500 - Local intravenous tolerance in the rabbit. 7 DEC 89
5.104.	RP 59500 - Local intravenous tolerance in the rabbit. Influence of rinsing volumes of a 5 % glucose solution. RPR/RD/CRVA/SM 538, 17 JUN 91
5.105.	RP 57669/RP 54476 - Local intravenous tolerance of a 10 mg/ml solution in the rabbit. Influence of filtration of the solution, of a post-infusion venous rinsing and of the injection rate. RPR/RD/CRVA/SM 599, 16 MAR 92
5.106.	RP 59500 - Local paravenous intradermal tolerance in the rabbit. 7 DEC 89
5.107.	RP 59500 - Local intra-arterial tolerance in the rabbit. 4 DEC 90
5.108.	RP 59500 - Local intra-arterial tolerance in the rabbit. 10 JAN 91
5.109.	RP 59500 - Comparison of vascular tolerance after a single intravenous injection in male rats and rabbits - Preliminary study. RPR/RD/CRVA/SM 95-0222, 14 DEC 95
5.110.	RP 57699/RP 54476 (30/70) - An exploratory study of venous tolerance in rhesus monkeys. 15 FEB 96
5.111.	RP 57699/RP 54476 (30/70) - Comparison of intradermal local tolerance of four salts (Methanesulfonate, gluconate, lactate and hypochloride) in rabbits. RPR/RD/DS/CRVA 92-3710, 4 JUL 96

5.112.	RP 57699/RP 54476 (30/70) (Synercid®)- Single-dose intravenous exploratory study of venous tolerance in mice - Effects of formulations, N-acetylcysteine, glutathione and antihistamines RPR/RD/DS/CRVA 96-0146, 30 MAY 96
5.113.	RP 57669/RP 54476 (30/70) (Synercid®)- Exploratory venous toxicity studies after a single intravenous injection in male rats - Effects of different formulations, N-acetylcysteine and antihistamines. RPR/RD/DS/CRVA 96-0150, 26 JUN 96
5.114.	RP 57669/RP 54476 (30/70) (Synercid®) : Exploratory intradermal tolerance study after a single administration in rabbits. Effect of different formulations and N-acetylcysteine. RPR/RD/DS/CRVA 95-0331, 4 JUL 96
5.115.	RP 59500 - Anaphylactic shock in the guinea pig. RPR/RD/CRVA/SM 537, 17 JUN 91
5.116.	RP 59500 - Study of the compatibility and hemolytic potential in human blood. 18 DEC 89
5.117.	RP 59500 - In-vitro study of the compatibility in human plasma. Comparison with vancomycin, teicoplanin, erythromycin, cefotetan and formyl cefamandole. 5 APR 91
5.118.	RP 57669/RP 54476 (30:70) - Cytotoxicity in rat and human hepatocytes in primary culture. RPR/RD/CRVA/SM 93-0174, 5 JAN 95
5.119.	RP 57669/RP 54476 (30/70) mesylate - Effect of glutathione depletion on liver toxicity parameters after single intravenous administration in male rats. RPR/RD/CRVA/SM 92-3964, 27 FEB 95
5.120.	RP 57886 - Acute toxicity study in the mouse by intravenous route - Exploratory study. 27 AUG 90
5.121.	RP 69991: Acute toxicity study in the mouse by intravenous route - Exploratory study. 1 OCT 90
5.122.	RP 57669/RPR 116367 - Bacterial reverse mutation test. RPR/RD/CRVA/SM 95-0188, 4 AUG 95
5.123.	RP 57669 and RP 57669/RPR 116367 - Single-dose intravenous toxicity study in rats. RPR/RD/CRVA/SM 95-0147, 12 SEP 95
5.124.	RP 57669 - Bacterial reverse mutation test Batch 16 (P95022V). RPR/RD/CRVA/SM 95-0148, 12 OCT 95

5.125.	RP 57669 - Single-dose intravenous toxicity study in rats (comparison of 2 batches: 11 and 16). RPR/RD/CRVA/SM 95-0146, 12 SEP 95
5.126.	RP 54474A - Acute toxicity in the mouse by intravenous route - Exploratory study. 30 MAR 90
5.127.	RP 60182 - Acute toxicity study in the mouse by intravenous route - Exploratory study. 1 OCT 90
5.128.	RP 60183 - Acute toxicity study in the mouse by intravenous route - Exploratory study. 4 OCT 90
5.129.	RP 57669/RP 54476, RP 75646 and RP 75645 - Single-dose intravenous lethality study in mice. RPR/RD/CRVA/SM 94-0118, 8 JUL 94
5.130.	RP 54476A: In-vitro gene mutation test on *Salmonella Typhimurium* strains. RPR/RD/CRVA/SM 94-0199, 5 OCT 94
5.130.A	RP 57669/RP 54476 (30/70), RP 57669 and RP 54476 : Comparative venous toxicity study after a single one-hour infusion in the tail vein of male rats. 26 May 97
5.130.B	RP 57669/RP 54476 (30/70) : Exploratory venous toxicity study in monkeys. 07 May 97
5.130.C	RP 57669/RP 54476 (30/70) (Synercid®): Single-dose intravenous toxicity study in association with diphenhydramine in male rats. 14 NOV 96.
5.130.D	RP 57669/RP 54476 (30/70) (Synercid®) : Effect of citrate buffer solutions (pH 4.0) on venous tolerance after a single I.V. injection in mice. 15 MAY 97
5.130.E	RP 57669/RP 54476 (30/70) (Synercid®) : Exploratory venous toxicity studies after a single intravenous injection in male rats. Effect of buffer solutions (5 % PS80/Neutral Phosphate buffer and acidic citrate buffer) 06 DEC 96
5.130.F	RP 57669/RP 54476 (30/ 70) (Synercid®). Exploratory venous toxicity study in monkeys. Effect of acidic citrate buffer (25 mM; pH 4). 03 JUN 97
5.130.G	RP 57669/RP 54476 (30/70): 2-Week O.D.D. intravenous toxicity study in monkeys using an acidic citrate buffered formulation 18 JUN 97

5.130.H	An Antigenicity Study of RP 57669/RP 54476 (30/70). 03 MAR 97
5.130.I	Quinupristin/Dalfopristin (RP 57669/ RP 54476) : Interaction with mammalian cell-free translation. RPR/RD/DISC/BIOL/CRVA 877 , 13 JAN 97

Document Number	Title
5.131.	Method and validation of HPLC assays for determination of RP 57669, RP 54476 and RP 12536 in human blood Report RPR/DD 92-07, December 1992
5.132	Simultaneous determination of RP 57669, RP 69012, RPR 100391, RP 54476 and RP 12536 in monkey plasma by high-performance liquid chromatography Report RPR DMPK/FR/2093, September 30, 1996 (Addendum to the report DMPK/Fr/2027).
5.133.	Pristinamycin (RP 59500) Injectable Streptogramin - Microbiological Assay of RP 59500 in blood - Method and validation RPR/RD/IBP/An DL-151, 14 March 1991
5.134.	Investigation of the stability of RP 54476-RP 57669 Report RPR/DD 91-54, 20 November 1991
5.135.	Long term stability of RP 57669, RP 54476 and RP 12536 in whole blood Report RPR/DD 93-132, 10October 1993
5.136.	Stability of ^{14}C-RP 57669 and ^{14}C-RP 54476 25 March 1996
5.137.	Pharmacokinetics of RP 57669/RP 54476 in the rat after single intravenous administration (one-hour infusion of 5, 15, 25 and 43 mg/kg doses and bolus of 15 mg/kg dose) 20 september 1995
5.138.	91-Day toxicokinetic study of RP 57669/RP 54476 (30/70 mesylate) after one-hour infusion in the unrestrained rat given 5, 10 and 25 mg/kg doses t.i.d. 25 September 1995
5.139	RP 57669/RP 54476 pharmacokinetic study in the rat following IV bolus at 6 and 12 mg/kg and 1-hour infusion at 25 mg/kg Report RPR/CPD/DMPK Fr. N° 2041, May 1996

5.140.	Pharmacokinetics of RP 57669/RP 54476 in the monkey after single intravenous administration (one-hour infusion of 10, 20, 40 and 120 mg/kg doses and bolus of 40 mg/kg dose) 19 september 1995
5.141.	90-Day toxicokinetic study of RP 57669/RP 54476 (30/70 mesylate)administered t.i.d. by intravenous infusion to Rhesus monkeys 20 June 1995
5.142.	Pharmacokinetics in the anaesthetized dog after a one-hour infusion dose of RP 59500 (22.4 mg/kg) 27 June 1991
5.143.	Pharmacokinetics in the anaesthetized micropig after a one-hour infusion dose of RP 57669/RP 54476 (22.4 mg/kg) 10 July 1995
5.144.	RP59500 - "A.D.E" studies in the rat at the dose of 6 mg/kg by intravenous route 4 July 1990
5.145.	Kinetic study of RP59500 in cynomolgus monkeys.
5.146.	Excretion, plasma kinetics and tissue distribution of total radioactivity in the Cynomolgus monkey following single intravenous administration of RP 57669 (30%) and ^{14}C-RP 54476 (70%) at a total dose of 10 mg.kg^{-1} 14 March 1994
5.147.	The excretion, plasma kinetics and tissue distribution of total radioactivity in the Cynomolgus monkey following single intravenous administration of ^{14}C-RP 57669 (30%) and RP 54476 (70%) at a total dose of 10 mg.kg^{-1} 8 December 1995
5.148.	28-Day intravenous toxicity study of RP 59500 in the albino rat followed by a 28-day recovery period May 1996.
5.149.	RP 57669and RP 54476 - Four-week toxicokinetics in the monkey by intravenous route following once-daily administration (RP 57669 : 1, 4 and 16 mg/kg doses - RP 54476 : 2.5, 10 and 25 mg/kg doses) 14 December 1989

5.150.	Four week toxicokinetics in the monkey by intravenous route following once daily administration (2, 6 and 30 mg/kg doses) 28 June 1990
5.151.	RP 57669 and RP 54476 Toxicokinetics during 28-day intravenous toxicology study in the Rhesus monkey (10, 20 and 40 mg/kg t.i.d. doses) 31 January 1994
5.152.	A 26-week toxicokinetic study of RP 57669/RP 54476 (30/70, w/w) administered tid by intravenous infusion to Rhesus monkeys. Report RPR/DMPK/FR/2087, October 1996.
5.153.	Toxicokinetic study in pregnant mouse by i.v. route April 1996
5.154.	RP 59500 : Teratology study in the rabbit May 1996
5.155.	Autoradiographic study of the tissue distribution of radioactivity in the rat following administration of [^{14}C]-labelled RP59500 by intravenous route 4 July 1990
5.156.	Tissular distribution of [^{14}C] RP59500 after a single intravenous administration to cynomolgus monkeys whole body autoradiographic studies.
5.157.	The disposition of ^{14}C-RP 57669 (30%) and RP 54476 (70%) in the rat following repeated intravenous administration once daily for 14 days 5 February 1996
5.158.	Study of the transplacental passage of RP59500 in the pregnant rat. (July 1989)
5.159.	^{14}C-RP 59500 (^{14}C-RP 57669/RP 54476) - Radioactivity milk transference in the lactating rat following single intravenous administration at 6 mg.kg^{-1} 9 August 1995
5.160	*In vivo* bactericidal activity of RP 59500 (quinupristin/dalfopristin), in *streptococcus pneumoniae* mouse pneumonia. ICAAC 1996 - Rhône-Poulenc Rorer S.A., Centre de Recherche de Vitry-Alfortville, 94403, Vitry, France- RPR/RD/DISC/BIOL CRVA 814 18/06/96

5.161.	In vivo activities and penetration of the two components of the Streptogramin RP 59500 in cardiac vegetations of experimental endocarditis (1994)
5.162.	Interstitial fluid diffusion of RP 59500 in a rabbit tissue cage model (ENG) 31st Interscience conference on antimicrobial agents and chemotherapy (ICAAC), Chicago, 29/9-2/10/1991, 249 AB:903; 1st International conference on the macrolides, Azalides and streptogramins,
5.163.	Cellular uptake and intracellular bactericidal activity of RP 59500 in murine macrophages
5.164.	Activities of RP 59500 (Quinupristin/Dalfopristin) and macrolides against *Legionella Pneumophila* in a model of J774 Macrophages in relation to their cellular accumulation.
5.165.	In vitro plasma protein binding of Quinupristin (RP 57669) and Dalfopristin (RP 54476) in rat, monkey and man Report RPR/CPD/DMPK Fr. N° 1992, April 12,1996.
5.166.	RP59500 : Biliary excretion and metabolic profiles in conscious male rats after intravenous administration of a dose of 6 mg/kg 4 July 1990
5.167.	RP59500 Biotransformation in rats at a dose of 6 mg/kg by intravenous route version 2 (23/2/90)
5.168.	RP59500 : Metabolic Profiles in monkeys at the 6 mg/kg dose administered by intravenous route 1) Study of [^{14}C]-RP 57669 metabolism, 2) study of [^{14}C]-RP 54476 metabolism. 8 July 1991
5.169.	*In vitro* metabolism of ^{14}C-RP 57669 and ^{14}C-RP 54476 in mouse, rat, monkey and human liver subcellular fractions 8 October 1992

5.170	In vitro bacteriostatic activity of two metabolites of RP 57669 (RP 69012,RPR 100391)Appendix VII of the Pharmacokinetic report of the final study report February 24,1993
5.171	In vitro bacteriostatic activity of metabolites of RP 54476(RP 12536) Appendix VII of the Pharmacokinetic report of the final study report February 24,1993
5.172.	Effects of RP59500 on the metabolic enzymes of rat liver. (6/07/90)
5.173.	Effects of Synercid (RP 59500) on human liver cytochrome P450 isoenzymes in vitro RPR/DMPK 2026, 10 April 1996
5.174.	RP 57669/RP 54476 30/70 (Synercid®) - Effect on cyclosporin a metabolism in human liver microsomes in vitro RPR/RD/DISC/DD/CRVA N°5, 13 December 1995
5.175.	RP 59500 - Enterohepatic cycle in male rat following single intravenous administration of ^{14}C-RP 57669 (30%) and RP 54476 (70%) at a total dose of 6 mg.kg^{-1} 25 September 1992
5.176.	RP59500 - Enterohepatic cycle in male rat following single iv administration of RP 57669 (30%) and [^{14}C]-RP 54476 (70%) at a total dose level of 6 mg.kg^{-1}. 27 August 1992
5.177	Evaluation of in vitro stability / transformation of RP 57669, RP 54476 and their main known metabolites in human blood , human plasma and rat blood at room temperature 31 OCT 96

PRECLINICAL SAFETY INFORMATION

Some of the pharmacology/toxicology information on the compound(s) has been reviewed previously in the IND submissions. Most of the toxicology studies were conducted during the late 1980s and early 1990s at the sponsors facility in France, and at contract laboratories in France, England, and Canada. The toxicology studies were conducted in compliance with the applicable Good Laboratory Practice guidelines, and included analytical confirmation of the test substances and dosing solutions. Unless specified otherwise, the toxic effects described in this review (increases, decreases, histologic changes, etc.) are considered to be statistically and biologically significant.

Acute Toxicity

Mice

In studies in mice, Synercid and the three components of quinupristin were administered intravenously in a single dose. The mice were observed for 14 days for signs of toxicity. Mortalities occurred within 24 hours of dosing. The following median lethal doses were reported:

Synercid: LD50: 107 mg/kg (both sexes combined)
RP 68888: LD50: 76 mg/kg (both sexes combined)
RP 60844: LD50: 50 mg/kg (both sexes combined)
RP 67648: LD50: >122 mg/kg (males)
98-122 mg/kg (females)

The signs of toxicity seen in these mice were ataxia, dyspnea, decreased motor activity, prostration, and convulsions.

In another study in mice, it was determined that cumulative doses of Synercid greater than the median lethal dose, could be tolerated, if administered in divided doses in one day. For example, there were no deaths in a group of 10 mice (5 male, 5 female) that received three injections (70 mg/kg) of Synercid at three hour intervals (210 mg/kg total).

Rats

Synercid, quinupristin and dalfopristin were tested in rats. The following median lethal doses were reported after intravenous administration:

Synercid: LD50: 28 mg/kg (both sexes combined)
Quinupristin: LD50: 18.4 mg/kg (both sexes combined)
Dalfopristin: LD50: 117 mg/kg (both sexes combined)

Signs of toxicity in the rats were ataxia, dyspnea, decreased motor activity, prostration, and convulsions.

Additional studies in rats indicated that Synercid was better tolerated if it was given in divided doses, or if a slower rate of

injection was used, or if it was given as an infusion.

Monkeys

Acute studies were also conducted in monkeys. Quinupristin was administered intravenously to cynomolgus monkeys (2/sex/group) in a single dose of either 0, 12.5, 25, or 50 mg/kg. No signs of toxicity were seen at the low dose. Ataxia and decreased motor activity occurred after doses of 25 and 50 mg/kg. Phlebitis of the injected vein was seen microscopically, mainly in the 50 mg/kg group. There were no deaths in this study.

In another study, dalfopristin was administered intravenously to cynomolgus monkeys (2/sex/group) in a single dose of either 0, 30, 100, or 300 mg/kg. Other than one episode of vomiting, no signs of toxicity were seen at the low dose. Salivation, emesis, ptosis, ataxia, decreased muscle tone, and decreased motor activity occurred after doses of 100 and 300 mg/kg. Tremors were seen in the 300 mg/kg group, and there was one death in this group. Phlebitis, perivenous ulceration, and necrosis were seen microscopically in the high-dose group.

In a pilot study, Synercid was administered intravenously to one female cynomolgus monkey at a dose of 200 mg/kg, and to two females at 150 mg/kg. The animal dosed at 200 mg/kg died; the two animals dosed at 150 mg/kg collapsed, but survived. In the definitive study, Synercid was administered intravenously to cynomolgus monkeys (2/sex/group) in a single dose of either 0, 50, 90, or 175 mg/kg. In this study, all of the animals dosed at 175 mg/kg died within 24 hours of dosing, but the dose of 90 mg/kg was well-tolerated. In a subsequent study, it was determined that a total daily dose of 180 mg/kg could be tolerated if it was administered as two doses of 90 mg/kg separated by an interval of six hours.

Subchronic Toxicity

Synercid, quinupristin, and dalfopristin were evaluated in one-month intravenous toxicity studies in Sprague-Dawley rats (the more sensitive rodent species) and in cynomolgus and rhesus monkeys. The studies were conducted using standard experimental designs and methodology. Evaluations for treatment-related effects in these studies were based on clinical observations, body weights, food consumption, ophthalmoscopy, hematology, blood chemistries, urinalysis, gross pathology, organ weights, microscopic histopathology, and limited electron microscopy. Electrocardiograms were also measured in monkeys.

Rats

Synercid was administered intravenously at doses of 0, 2, 6, or 18 mg/kg/day for one month (15 rats/sex/group). Elevated levels of alanine aminotransferase, aspartate aminotransferase, and lactic

dehydrogenase occurred, mainly in the high-dose group. Microscopically, renal cortical tubular atrophy and dilation were seen in all treated groups. There were 12 deaths in the study, but many of the deaths were attributed to the blood sampling procedure; six of the deaths were in the high-dose group, and these appeared to be treatment-related. The only other changes that were clearly treatment-related occurred at the injection site, and consisted of swelling, exfoliation, and ulceration of the tail.

Quinupristin was administered intravenously at doses of 0, 1, 4, or 8 mg/kg/day for one month (10 rats/sex/group). Elevations in aspartate aminotransferase, creatine phosphokinase, and lactic dehydrogenase occurred in the mid and high-dose groups. Ataxia, dyspnea, and decreased activity were seen in high-dose animals. Microscopically, a renal tubular basophilia was seen in some high-dose animals. There were four deaths in this study; one in the mid-dose group, and three in the high-dose group. All four deaths appeared to be treatment-related.

Dalfopristin was administered intravenously at doses of 0, 2.5, 10, or 50 mg/kg/day for one month (10 rats/sex/group). Treatment-related effects occurred only in the high-dose group. These included decreases in erythrocyte counts, hemoglobin, and hematocrit, changes at the injection site, and seven deaths.

Monkeys

Synercid was administered intravenously to cynomolgus monkeys at doses of 0, 2, 6, or 30 mg/kg/day for one month (3/sex/group). Animals in the high-dose group displayed salivation, retching, emesis, and decreased food consumption. This group also had decreases in erythrocyte counts, hemoglobin, and hematocrit, and slightly prolonged electrocardiographic QT intervals. Bruising, swelling, exfoliation, ulceration, and serous discharge occurred at the injection site, but there were no deaths. Skeletal muscle, atrial cardiac muscle, and ventricular cardiac muscle were examined with light and electron microscopy, and no histologic or ultrastructural changes were found.

Quinupristin and dalfopristin were evaluated in another one-month study in cynomolgus monkeys. Quinupristin was administered at doses of 0, 1, 4, or 16 mg/kg, while dalfopristin was administered at doses of 0, 2.5, 10, or 25 mg/kg. The only effects that could be attributed to treatment, were changes at the injection site, similar to those described above. There were no hematology or electrocardiographic changes.

In another study, a three times per day dosing regimen of Synercid was investigated in rhesus monkeys. Synercid was administered as an intravenous infusion at doses of 0, 10, 20, or 40 mg/kg three times daily (0, 30, 60, or 120 mg/kg/day). Animals in the high-dose group showed decreased food consumption, signs of anemia

(decreases in erythrocyte counts, hemoglobin, hematocrit) and changes at the infusion site. There were no deaths.

Chronic Toxicity

Rats

Synercid was evaluated in rats in studies of three and six month duration. In one three-month study, Synercid was administered to Sprague-Dawley rats (15/sex/group) in a single intravenous injection at doses of 0, 2, 6, or 12 mg/kg/day. Extra animals (10/sex/group) were carried in the control and high-dose groups, to evaluate reversibility of the findings during a treatment-free recovery phase. There were two deaths in the high-dose group, and these were probably treatment-related. Signs of toxicity occurred mainly in the high-dose group and consisted of changes at the injection site (reddening, bruising, swelling, thickening, exfoliation, ulceration, and scab formation) decreases in erythrocyte counts, hemoglobin, and hematocrit, and increases in plasma urea nitrogen. Kidney weights (absolute and relative) were increased, and signs of renal pathology were observed microscopically (vacuolation and dilatation of cortical tubular epithelium, with lymphocytic infiltration). Some of these effects were also seen in the mid-dose group, although to a lesser extent. No ultrastructural changes were detected in skeletal muscle, atrial cardiac muscle, or ventricular cardiac muscle when these tissues were examined with light and electron microscopy. Virtually all of the toxicity was found to be reversible during the recovery phase of the study.

In another three-month study in rats, Synercid was administered as a one hour intravenous infusion, through cannulas implanted into the femoral vein. The doses were 0, 5, 10, or 25 mg/kg three times per day (0, 15, 30, or 75 mg/kg/day). Signs of toxicity consisted of sedation, piloerection, hunched posture, decreases in erythrocytes, hemoglobin, and hematocrit, increases in reticulocytes, alanine aminotransferase, and aspartate aminotransferase, and signs indicative of vascular irritation. Extramedullary hematopoiesis was observed microscopically in liver and bone marrow. Most of these signs occurred in all three treated groups. The mortality rate in this study was about 17%, but many of the deaths were attributed to venous complications arising at the site of the indwelling catheter.

A six-month study of Synercid in rats was conducted at a different contract laboratory, using the same three infusions per day dosing regimen. The same dose levels were used in the six-month study, and in general, the findings in the six-month study were similar to those in the three-month study described above.

Monkeys

Synercid was administered as a single intravenous injection to cynomolgus monkeys at doses of 0, 2, 6, or 20 mg/kg/day for three months (4/sex/group). There were no deaths in the study. Toxic effects were relatively mild and, for the most part, were limited to the high-dose group. The signs included salivation, subdued behavior, transient decreases in blood pressure, increases in alanine aminotransferase, increased kidney weights, an orange coloration of the urine, and injection site changes as described previously.

Three-month studies of Synercid were also conducted in rhesus monkeys, in which the compound was administered three times per day, as an intravenous infusion using an indwelling catheter. The doses were 0, 10, 20, or 40 mg/kg three times daily (0, 30, 60, or 120 mg/kg/day). In one of these two studies, the high dose was reduced from 120 to 90 mg/kg/day because of excessive toxicity. The mortality rate ranged from 50-70% in the high-dose groups. The toxic signs seen in these studies were similar to the signs seen in some of the preceding studies. These included emesis, emaciation, anemia, increased transaminases, venous irritation, and several dermatological changes. The skin changes were manifested as dry scaly skin, cutaneous crusts, discoloration, erythema, edema, blisters, and loss of fur. Changes in the dermis and epidermis were confirmed microscopically (infiltration of lymphocytes, leukocytes, acanthosis, parakeratosis). Microscopic changes were also seen in the renal tubular epithelium (tubular dilatation, basophilia, inflammation). Other findings in these animals included splenic and thymic atrophy, and inflammation of the vena cava in the vicinity of the catheter tip.

A six-month study was conducted in rhesus monkeys, using the same experimental design, but with lower doses. In the six-month study, the doses of Synercid were 0, 5, 10, or 15 mg/kg infused intravenously three times per day (0, 15, 30, or 45 mg/kg/day). Less toxicity was seen in this study, although some trends occurred that were similar to the effects seen at higher doses, in the three-month studies.

Reproductive Toxicity

Fertility and Reproductive Function (Segment I type study)

Synercid was administered intravenously to Sprague-Dawley rats (26/sex/group) at dose levels of 0, 2, 6, or 12 mg/kg/day. The males were dosed for at least 10 weeks before mating, while females were dosed for at least two weeks prior to mating. Dosing continued for both sexes throughout the mating period, gestation, and lactation. Males were sacrificed, and the testes, seminal vesicles, epididymides, and prostate gland were removed and

weighed. Approximately 50% of the pregnant females were sacrificed on gestation day 20, and the reproductive tract was removed and examined for corpora lutea, implantations, and resorption sites. The remaining females were allowed to deliver normally, and rear the offspring (the F1 generation). The physical development, behavior, and reproductive ability of the F1 generation were evaluated.

Treatment with Synercid had no effect on male reproductive organ weights, or on female mating or fertility. There was also no effect on the F1 generation with regard to physical activity, auditory function, visual function, learning ability, or reproductive performance.

Teratogenicity and Embryofetal Development (Segment II type study)

Teratology studies were conducted in mice, rats, and rabbits. Synercid was administered intravenously to all three species (CD-1 mice, Sprague-Dawley rats, New Zealand albino rabbits) during the period of organogenesis. In mice, doses of 0, 10, 20, or 40 mg/kg/day were administered during days 6-15 of gestation. In rats, doses of 0, 2, 6, or 18 mg/kg/day were administered during days 6-15 of gestation. In rabbits, doses of 0, 2, 6, or 12 mg/kg/day were administered during gestation days 6-18. (Higher doses were used in range-finding studies).

Mice were sacrificed on day 18 of gestation, rats were sacrificed on day 20 of gestation, and rabbits on gestation day 29. Uterine contents were removed, fetuses were examined, and any fetal abnormalities were recorded. Some of the fetuses were placed in [redacted] for visceral examination, while the remaining fetuses were stained with [redacted] for skeletal examination.

A small number of anomalies/abnormalities were seen in all three species. These included (but were not limited to) lower fetal weights, small fetuses, delayed bone ossification, cleft palate, and exencephaly in mice, extra ribs and vertebrae in rats, and decreased ossification and spina bifida in rabbits.

Small numbers of abnormalities occurred in both control and treated groups in these studies, but the incidence appeared to be slightly higher in the treated groups. Because of the lack of a dose-response relationship, and because some of the abnormalities had also been seen in historical control animals from previous studies, it was not possible to attribute the effects to drug treatment.

Prenatal and Postnatal Development (Segment III type study)

This study was designed to evaluate the effects of the compound on the development of newborn animals. Synercid was administered intravenously to four groups of pregnant Sprague-Dawley rats (22-25 animals per group). The dose levels were 0, 2, 6, or 18 mg/kg/day,

and the doses were administered starting on day 15 of gestation, throughout lactation, and until postpartum day 21. The dams were allowed to deliver normally. At the appropriate age (postpartum days 4-51) the physical, functional, and behavioral development of the pups was determined. Physical development was measured by pinna detachment, incisor eruption, eye opening, and sexual maturity. Functional development was measured by the righting reflex, pupillary reflex, auditory startle response, swimming ability, etc. Behavioral tests included exploratory activity, locomotor activity, learning and memory tests.

There were no treatment-related effects on pregnancy rate, gestation length, post-implantation loss, litter size, or pup survival. Also, no effects were seen in pups with regard to any of the developmental parameters tested.

Genetic Toxicity

[redacted]

When tested in a Chinese hamster ovary cell line for clastogenic potential, dalfopristin (RP54476) was associated with a statistically significant increase in the percentage of cells with chromosomal aberrations, and with an increase in the mean number of chromosome aberrations per cell. The aberrations seen most frequently in this cell line (CHO-K1) were chromatid gaps, breaks, and fragments, chromosome gaps and breaks, and acentric fragments.

When quinupristin (RP57669) and Synercid (RP59500) were tested in the CHO-K1 cell line, some very slight increases in the percentage of cells with aberrations and the mean number of aberrations were observed, but the increases were not statistically significant.

The CHO-K1 cell line was also used to evaluate the mutagenic potential of these agents. The HGPRT test measures a mutation at the site of the gene that codes for the enzyme hypoxanthine-guanine phosphoribosyl transferase in these cells. Dalfopristin, quinupristin, and Synercid did not induce mutations in this assay when tested either in the presence or absence of metabolic activation.

[redacted]

When tested in the bacterial reverse mutation (Ames) assay, dalfopristin, quinupristin, and Synercid were non-mutagenic with or

without metabolic activation.

Dalfopristin, quinupristin, and Synercid did not induce DNA damage and repair, as measured by unscheduled DNA synthesis, in a primary culture of rat hepatocytes.

Safety Pharmacology

A series of safety pharmacology experiments were conducted to predict the potential of the compound(s) to affect the various organ systems of the body. These tests included:

electrocardiograms in monkeys
blood pressure in rats, dogs, and monkeys
action potentials in guinea pig cardiac Purkinje fibers
histamine release in rats
bleeding times in rats
coagulation times in rats
prostaglandin production during blood coagulation
in vitro receptor binding profile
behavior screens in mice and rats
hexobarbital sleeping time in mice
pentylenetetrazole-induced seizures in mice
electroencephalograms in rats
body temperatures in mice and rats
urinary output in rats
bile secretion in rats
gastric acid secretion in rats
gastrointestinal transit time in rats

Treatment with Synercid frequently resulted in decreases in blood pressure in the rat, dog, and monkey models, and the hypotension was often associated with histamine release. Pretreatment with an antihistamine blocked the hypotensive effects. Synercid had little or no effect on the other parameters.

Pharmacokinetics

The following pharmacokinetic data was obtained following intravenous administration of Synercid to rats:

Blood pharmacokinetics* of Synercid in rat after an one-hour infusion at 5, 15, 25 and 43 mg/kg^{-1}

N°	Sex	Dose mg/kg^{-1}	t_{max} h	C_{1h} µg.ml^{-1}	AUC(o - lqc) h.µg.ml^{-1}	AUC h.µg.ml^{-1}	$t_{1/2}$ h	CL l.h^{-1}.kg^{-1}	Vd l/kg^{-1}
RP	M	5	1	0.21 ± 0.06	-	-	-	-	-
57669	F	5	1	0.08 ± 0.07	-	-	-	-	-
	M	15	1	0.94 ± 0.10		-	-	-	-
	F	15	1	0.38 ± 0.33		-	-	-	-
	M	25	1	1.57 ± 0.21	1.11	1.16	0.46	6.44	4.27
	F	25	1	0.34 ± 0.30	0.31	0.37	0.46	20.16	13.33
	M	43	1	3.48 ± 0.28	2.39	2.68	0.73	4.81	5.06
	F	43	1	2.36 ± 1.23	1.67	1.75	0.54	7.37	4.74
RP	M	5	1	0.24 ± 023	-	-	-	-	-
54476	F	5	1	0.36 ± 0.06	-	-	-	-	-
	M	15	1	2.64 ± 0.40	2.27	2.39	0.68	4.40	4.33
	F	15	1	1.41 ± 0.70	1.54	1.72	0.79	6.10	6.93
	M	25	1	4.25 ± 0.70	2.97	3.08	0.46	5.68	3.80
	F	25	1	0.80 ± 0.68	0.93	1.03	0.43	17.00	10.62
	M	43	1	8.43 ± 0.91	4.98	5.18	0.63	5.81	5.25
	F	43	1	5.14 ± 2.78	3.59	3.71	0.48	8.12	5.62

** : mean ± SD, n = 3 animals/sex/time.*

AUC = area under the concentration-time curve
lqc = last quantified concentration

When Synercid was given to cynomolgus monkeys, the following data was generated:

Blood pharmacokinetics* of Synercid in monkey after one-hour infusion at 10, 20, 40 and 120 mg/kg doses of RP 57669/RP 54476 (30/70)

N°	Dose mg/kg^{-1}	T_{max} h	C_{max} h	AUC(0-t) h.µg.ml^{-1}	AUC h.µg.ml^{-1}	$t_{1/2}$ h	Cl l/kg^{-1}.h^{-1}	Vd l/kg^{-1}
RP57669	10	1.00	1.78	1.66	1.75	0.38	1.78	0.96
			± 0.60	± 0.37	± 0.38	± 0.05	± 0.44	± 0.17
	20	1.00	3.53	3.59	3.74	0.42	1.63	0.98
			± 0.56	± 0.56	± 0.53	± 0.04	± 0.23	± 0.06
	40	1.00	10.42	12.29	12.69	0.51	0.98	0.71
			± 0.59	± 2.27	±2.35	± 0.06	± 0.22	± 0.16
	120	1.00	36.04	48.94	60.02	1.13	0.62	1.00
			± 8.50	± 8.66	± 9.36	± 0.24	± 0.09	± 0.28
RP54476	10	0.75	2.45	1.70	-	-	-	-
			± 0.88	± 0.24				
	20	0.75	3.45	2.84	3.09	0.29	4.54	1.93
			± 0.55	± 0.40	± 0.06	± 0.07	± 0.09	± 0.49
	40	1.00	10.92	9.66	9.02	0.24	3.12	1.08
			± 1.23	± 1.44	±0.78	± 0.04	± 0.27	± 0.08
	120	1.00	52.91	44.96	48.83	0.41	1.79	1.08
			± 13.55	± 11.85	± 11.76	± 0.07	± 0.44	± 0.42
RP12536	10	1.00	0.46	0.41	0.50	0.43		
			± 0.16	± 0.11	± 0.11	± 0.24		
	20	1.08	0.71	0.91	1.06	0.58		
			± 0.14	± 0.17	± 0.11	± 0.18		
	40	1.08	2.25	2.82	3.02	0.58		
			± 0.84	± 0.79	± 0.82	± 0.04		
	120	1.08	5.78	9.70	10.86	0.74		
			± 1.39	± 2.05	± 2.27	± 0.08		

- not available, * : mean+/- SD, n = 2/sex/dose

Following the intravenous administration of Synercid labeled with carbon-14, radioactivity could be detected in every tissue examined, with the highest concentrations appearing in the bile as shown below.

Levels of total radioactivity in selected tissues and organs in Cynomolgus male monkeys (n = 4) following single 0.2-hour iv infusion of ^{14}C-RP 57669 (30%) and RP 54476 (70%) at 10 mg/kg^{-1} dose. Results expressed as µg equiv. RP 57669.g^{-1}

Organ µg eq/g	1 hour	6 hours	24 hours	168 hours
Adrenal	3.94	0.18	0.10	0.03
Bile (ml^{-1})	1110.41	424.98	43.13	0.53
Bladder	15.84	0.32	0.10	0.01
Blood	0.59	0.20	0.05	0.01
Bone Marrow	0.56	0.13	0.08	0.03
Brain	0.01	0.01	*0.00	*0.00
Eye-pigmented	+	0.06	0.05	0.01
Remaining eye	+	0.14	0.06	0.01
Gall bladder	97.81	139.30	8.35	1.23
Heart	1.39	0.21	0.07	0.01
Hypophysis	+	1.15	0.30	*0.02
Kidney	4.34	5.45	3.07	0.61
Large Intestine	1.27	27.96	4.97	0.04
Liver	11.25	5.48	2.74	0.30
Lung	1.40	0.43	0.12	0.02
Lymph Nodes	2.37	0.30	0.17	0.04
Muscle	0.52	0.11	0.03	0.01
Pancreas	3.31	0.50	0.19	0.03
Prostate	19.74	0.42	0.08	0.02
Salivary Gland	3.42	0.93	0.28	0.02
Skin	0.77	0.35	0.15	0.03
Small Intestine	6.70	7.98	0.54	0.02
Spinal Cord	0.02	0.02	0.01	0.00
Spleen	1.81	0.41	0.12	0.04
Stomach	4.19	0.28	0.11	0.03
Testes	0.62	0.21	0.07	0.02
Thymus	1.65	0.37	0.10	0.02
Thyroid	0.89	0.15	0.08	0.01

+ = Sample missing

** = Results calculated from data less than 30 d.p.m. above background*

Biliary excretion represents the main route of elimination for Synercid. The majority of an intravenously administered dose was eliminated in the feces, as shown below for rats and monkeys.

Excretion in rats given a single IV 6 mg/kg dose of ^{14}C-RP 57669/RP 54476 or RP 57669/^{14}C-RP 54476. Results in % of dose

14C-product	RP 57669		RP 54476	
Sex	Male	Female	Male	Female
% in urine (0 - 24 h)	7.8 ± 1.5	6.6 ± 2.1	11.4 ± 1.5	6.6 ± 1.5
% in urine (0 - 168 h)	8.4 ± 1.5	7.2 ± 2.2	12.0 ± 1.5	7.2 ± 1.6
% in faeces (0 - 48 h)	76.4 ± 7.8	80.6 ± 4.1	59.3 ± 6.0	61.7 ± 7.0
% in faeces (0 - 168 h)	79.9 ± 6.0	84.9 ± 1.7	66.1 ± 2.6	67.1 ± 6.5
% in expired air (0 -48 h)	*	*	3.93	3.27
% Recovery at 96 hours	88.3	92.3	87.9	82.9

** : not significant*

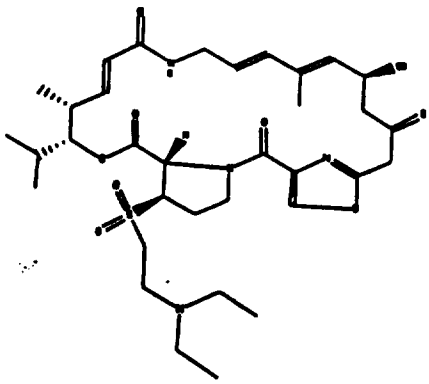
Excretion in Cynomolgus monkeys given a single IV 6 mg/kg dose of ^{14}C-RP 57669/RP 54476 or RP 57669/^{14}C-RP 54476. Results in % of dose

^{14}C-product	RP 57669		RP 54476	
Animal N°	89-221	89-222	89-223	89-224
% in urine (0 - 24 h)	21.55	14.06	16.49	20.96
% in urine (0 - 168 h)	23.97	17.65	18.04	24.08
% in faeces (0 - 48 h)	66.57	81.67	50.64	51.86
% in faeces (0 - 168 h)	72.53	89.09	82.53	71.46
% Recovery at 168 h	98.58	108.75	101.39	96.26

- = Not Determined

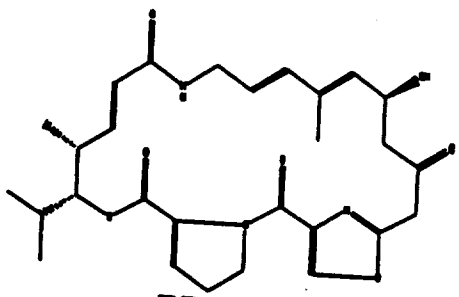
The metabolism of Synercid was similar in mice, rats, monkeys, and humans. Dalfopristin (RP 54476) is metabolized to RP 12536 as shown below. RP 12536 is conjugated with glutathione, and other metabolites are formed by ring cleavage.

Proposed metabolic pathways of RP 54476



RP 54476

↓



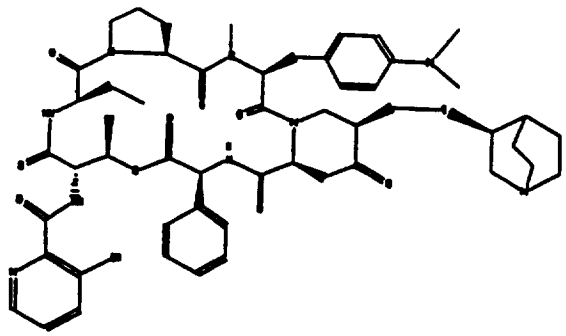
RP 12536

↓

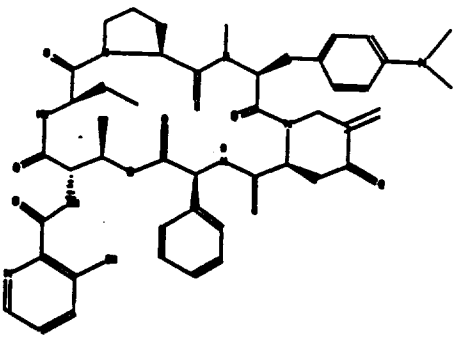
[**Gluthatione conjugate**] **+ unidentified drug-derived products formed by ring-cleavage**

Quinupristin is metabolized to RP 69012 and RP 100391 through the intermediate RP 50309 as shown below.

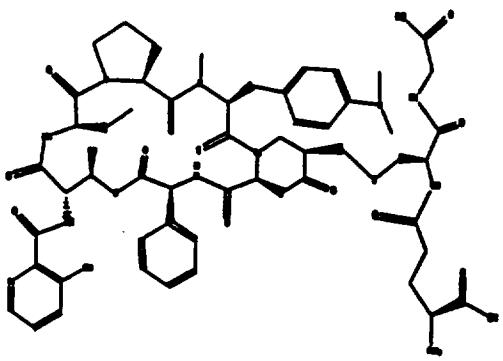
Proposed metabolic pathway of RP 57669



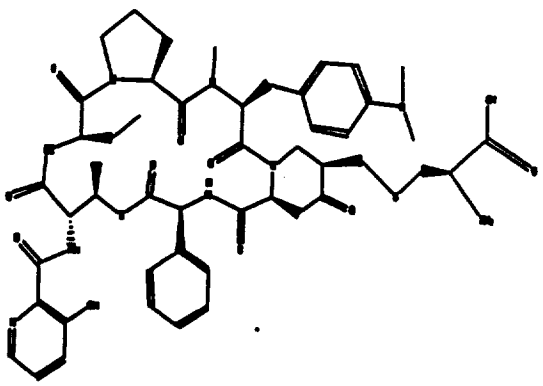
RP 57669



RP 50309



RP 69012



RPR 100391

When a single intravenous dose of Synercid, labeled with carbon-14, was administered to lactating rats, low levels of radioactivity were detected in both plasma and milk. Radioactivity could be detected in the milk for up to 72 hours after dosing.

Plasma protein binding was also studied using radioactive labeled Synercid. Following a single intravenous dose in male and female rats, quinupristin was 77-82% protein bound, while the binding of dalfopristin varied between 48-98%.

CONCLUSIONS/RECOMMENDATIONS FOR LABELING

Synercid is intended for intravenous administration, and virtually all of the toxicology studies were conducted by the intravenous route. The most common toxicity seen in the animal studies was toxicity at the injection site, such as swelling, bruising, exfoliation, phlebitis, ulceration, and necrosis. The severity of the vascular effects were related to the concentration of the dosing solution, and to the speed of injection or duration of infusion. Venous irritation has been the most troubling adverse event encountered in the clinical studies with Synercid, and has necessitated the discontinuation of dosing in some studies.

In the animal studies, rats were more sensitive than mice to the effects of Synercid. Rats and monkeys were chosen to evaluate the chronic toxicity of Synercid. Signs suggestive of damage to the liver, kidney, and blood-forming organs were seen in the systemic toxicology studies. The toxicity seen in the animal studies, occurred at doses that were close to the proposed human dose (7.5 mg/kg), suggesting that only a relatively narrow margin of safety exists with this therapy. For example, in the rat studies, the hepatic, renal, and anemic effects occurred in the high-dose groups, i.e. 18 mg/kg/day in the one-month study, and 12 mg/kg/day in the three-month study. In cynomolgus monkeys, the effects were seen at 30 mg/kg/day in the one-month study, and at 20 mg/kg/day in the three-month study. The toxicities were shown to be reversible after discontinuation of dosing. The vascular effects were also reversible.

Dalfopristin was associated with increased chromosomal aberrations in Chinese hamster ovary cells; Synercid and quinupristin gave ambiguous (but probably negative) results in this assay. However, Synercid, dalfopristin, and quinupristin were neither

Synercid did not produce treatment-related adverse reproductive or teratogenic effects in animal studies, although the decreased fetal weights were considered to represent a "fetal immaturity". No carcinogenicity study has been conducted with Synercid or either component.

From the standpoint of pharmacology/toxicology, approval of this NDA is recommended.

The following labeling is suggested:

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 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 12-18 mg/kg (approximately 0.3-0.4 times the human dose based on body-surface area).

Pregnancy: Teratogenic Effects: Pregnancy Category B: [redacted] 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), in rabbits at doses up to 12 mg/kg/day (approximately half the human dose based on body-surface area).

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, [redacted] should be used during pregnancy only if clearly needed.

Nursing mothers: [redacted]

OVERDOSAGE

Signs of acute overdosage may include dyspnea, emesis, tremors, and ataxia. Patients who receive an overdose should be carefully observed and given supportive treatment. Synercid is not removed by peritoneal dialysis, or by hemodialysis.

/S/
Kenneth Seethaler, R.Ph., Ph.D.,D.A.B.T.
Pharmacologist/Toxicologist HFD-520

cc: Original NDA 50-748
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/MO/A.Rakowsky
HFD-520/Micro/H.Silver
HFD-520/Chem/J.Timper
[redacted]

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1/27/98
1/28/98