CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-747

50-748

CHEMISTRY REVIEW(S)

DEC 3 0 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 50-747, Vancomycin resistant *entrococus faecium*
NDA 50-748, Skin and skin structure, [redacted]

CHEM.REVIEW #: 1 **REVIEW DATE:** 10/14/97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Original	9/5/97	9/8/97	12/1/97

NAME & ADDRESS OF APPLICANT:

Rhone-Poulenc Rorer Pharmaceuticals
500 Arcola Road
P.O.Box 1200
Collegeville, PA 19426-0107
(610) 454-8000

DRUG SUBSTANCE NAME

Established: Synercid (RP 59500)
USAN: quinupristin (RP 57669) / dalfopristin (RP 54476)
Code #: during the development of this product, the code number RP 59500 has been assigned to the combination of RP 57669 / RP 54476 in the fixed ratio of 30:70 w/w. In reports which have been previously issued the nomenclature for this product has been retained as RP 59500.

NDA 50-747: 1-P Drug Product.
NDA 50-748: 6-S Drug Product

PHARMACOLOGICAL CATEGORY/INDICATION:

Complicated skin and skin structure infections, [redacted]

NDA 50-747, Vancomycin resistant *entrococus faecium*
NDA 50-748, Skin and skin structure, [redacted]

ROUTE OF ADMINISTRATION:

Intravenous; 500 mg/vial, sterile, lyophilized

Rx/OTC: Rx

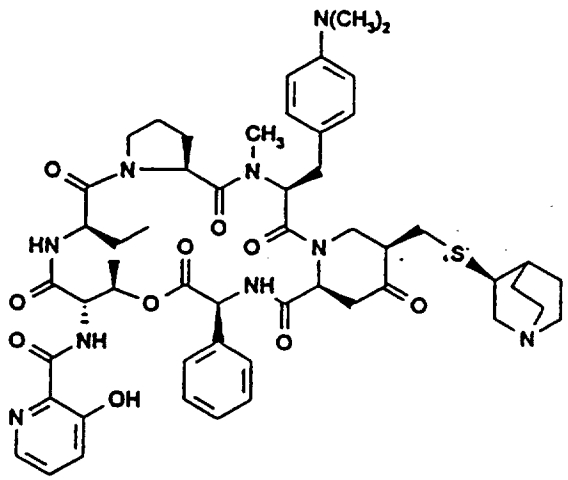
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

The drug product consists of two components: RP 57669 and RP 54476.

RP 57669

consists of a mixture of 3 peptide macrolactones; see drug substance description for complete description. The main component of quinupristin is molecular weight 1022.24, $C_{53}H_{67}N_9O_{10}S$:

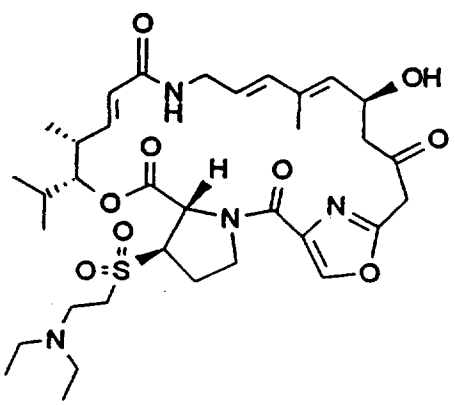
N-[(6R,9S,10R,13S,15aS,18R,22S,22S,24aS)-22-[p-(dimethylamino)benzyl]-6-ethyl-docosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-[[(3S)-quinuclidinylthio]methyl]-12H-pyrido[2.1-f]pyrrolo[2.1-f][1,4,7,10,13,16] oxapentaaza-cyclononadecin -9-yl]-3-hydroxypicolinamide;



RP 54476

this substance has molecular weight of 690.85, $C_{34}H_{50}N_4O_9S$:

(3R,4R,5E,10E,12E,14S,26R)-26-{[2-(diethylamino)ethyl]sulfonyl}-14-hydroxy-3-isopropyl-4,12-dimethyl-8,9,14,15,24,25,26,26a octahydro-3H-21,18-nitrilo-1H,22H-pyrrolo[2,1-c][1,8,4,19]dioxadiazacyclotetracosine-1,7,16,22(4H,7H)-tetrone



Related documents:

[redacted]

CONSULTS:

- Consult for microbiology for the sterilization of the product was sent to HFD-160 on 9/16/97. In addition, a follow-up consult was sent 9/25/97 regarding the aspects of fermentation of the starting material for synthetic steps.
- The EER has been requested, 9/17/97. The EER is not complete at this time.
- The firm has a statement of categorical exclusion for environmental impact.
- A consult to the labeling committee has be sent on 10/7/97 for the trade name.
- Method validation packages were provided to St. Louis and Philadelphia FDA laboratories on 10/7/97.

APPEARS THIS WAY
ON ORIGINAL

REMARKS/COMMENTS:

The drug product is a combination of two fermented products, each of which under separate synthetic processes and subsequently combined to make the drug product. Both components of the drug product, quinupristin and dalforpristin, are new molecular entities for an indication warranting 1-P priority review status.

CONCLUSIONS & RECOMMENDATIONS:

Recommend not approval based on the outcome of microbiology consults and inspections. The other aspects regarding chemistry, manufacturing, and controls are adequate. Recommend that the *drug product be given 18 months expiration dating* based on 12 months data for stability where the product is stored at 4°C, the storage temperature recommended for the drug product,.

/S/ 12/1/97
J. Timper

APPEARS THIS WAY
ON ORIGINAL

cc: Org. NDA 50-747; NDA 50-748
HFD-520/Division File
HFD-520/Katague/Team Leader, Chem /S/ 12/30/97
HFD-520/Timper/Chem
HFD-520/Rakowski/MO
HFD-520/Seethaler/Pharm
HFD-520/Sheldon/Micro
HFD-520/Dillon-Parker, Roche /Project managers
HFC-130/JAllen

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 50-747, Vancomycin resistant *entrococus faecium*

CHEM.REVIEW : Response by firm to approvable letter dated March 5, 1998.
REVIEW DATE: 8/14/98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	COMPLETED DATE
Correspondence	**5/5/98**	**5/6/98**	**8/14/98**

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REMARKS/COMMENTS:

There are two categories addressed in the approvable letter. The first pertains to inspection issue. The second pertains to the specifications for impurities/degradation limit specifications. The recent inspection uncovered that a specification for one related substance was set "in-house" to meet final specification for the drug product different from the NDA. The firm is required to place all drug product on stability until the current compliance issues are resolved. This will provide data to have a deeper understanding of the appropriate specifications if they need be changed. At this time it would not be productive to review the submission when other data will be sent to the division that will provide a better base to set specification.

CONCLUSIONS & RECOMMENDATIONS:

The current facilities for manufacturing the drug product are not approved. The data submitted in the current submission will be reviewed with the requested stability data. Specifications are better set with complete data at that time.

/S/ 8/14/98
J. Timper

CC: HFD-520
D. Katague, HFD-520 /S/ 8/14/98