Drugs of the Future 2006, 31(2): 107-113

CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.02.963570

Retapamulin

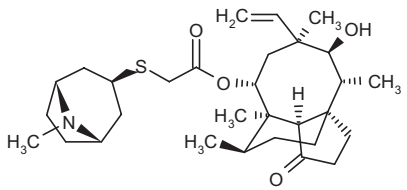
Pleuromutilin Antibiotic

Prop INN; USAN

SB-275833
Altabax®

(3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-2-(*exo*-8-Methyl-8-azabicyclo[3.2.1]octan-3-ylsulfanyl)acetic acid 5-hydroxy-4,6,9,10-tetramethyl-1-oxo-6-vinylperhydro-3a,9-propanocyclopentacycloocten-8-yl ester

Mutilin 14-(*exo*-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)acetate



$C_{30}H_{47}NO_4S$
Mol wt: 517.7645

CAS: 224452-66-8

EN: 276526

Abstract

Due to the emergence of multidrug-resistant microorganisms, research efforts are focusing on new classes of antibacterials with different mechanisms of action from those in clinical use. One such agent is retapamulin, a pleuromutilin derivative with a unique mechanism of action. Currently under development for the topical treatment of skin infections, retapamulin has shown no target-specific cross-resistance to commonly used antibiotics. In a number of *in vitro* studies, retapamulin demonstrated activity that was equivalent or superior to other common antibiotics against clinical isolates from skin and skin structure infections. The organisms susceptible to retapamulin include: *Streptococcus pyogenes, Streptococcus agalactiae*, β-hemolytic streptococci, viridans streptococci, *Staphylococcus aureus*, coagulase-negative staphylococci (including *Staphylococcus epidermidis*), *Propionibacterium* spp. (including *Propionibacterium acnes*), *Prevotella* spp., *Porphyromonas* spp. and *Fusobacterium* spp. However, retapamulin showed minimal or no activity against enterococci and Gram-negative bacilli. Importantly, retapamulin maintains its activity against organisms that are resistant to a number of antimicrobial agents, including methicillin, erythromycin, fusidic acid, mupirocin, azithromycin and levofloxacin. Evidence from multiple-step and single-step studies also suggests that retapamulin has a low potential to select for resistant mutants in *S. pyogenes* and *S. aureus*.

Synthesis

Reaction of the natural antibiotic pleuromutilin (I) with methane sulfonyl chloride by means of either TEA or DIEA in either CH_2Cl_2 or methyl isobutyl ketone provides the corresponding mesylate derivative (II) (1), which is submitted to nucleophilic substitution with *exo*-8-methyl-8-azabicyclo[3.2.1]octan-3-thiol (III) by means of either tetrabutylammonium hydrogensulfate in CH_2Cl_2/H_2O and NaOH at pH 12.5 (1) or potassium *tert*-butoxide in ethanol (2). Scheme 1.

The azabicyclic thiol derivative (III) can be prepared by different ways:

1) Mitsunobu reaction of *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (IV, tropine) with triphenylphosphine, diisopropyl azodicarboxylate and thioacetic acid in dry THF (2). Scheme 1.

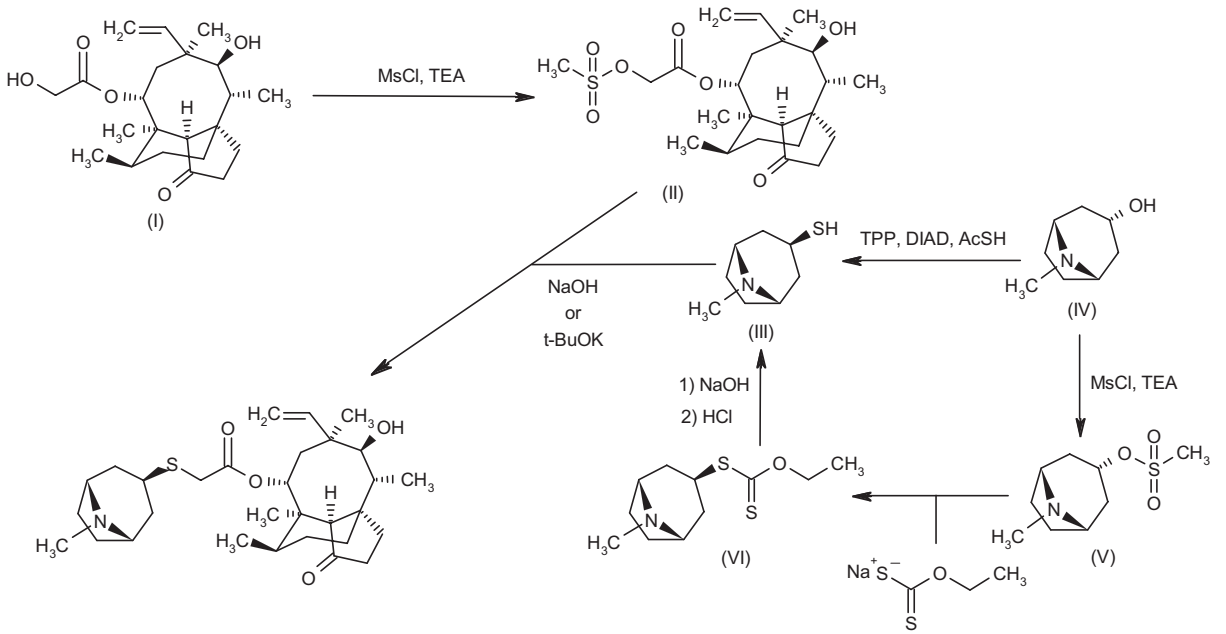
2) Treatment of *endo*-8-methyl-8-azabicyclo[3.2.1]-octan-3-ol (IV, tropine) with methane sulfonyl chloride and either TEA or DIEA in CH_2Cl_2 yields tropine-3-mesylate (V), which after nucleophilic substitution with sodium ethyl dithiocarbonate in toluene affords the intermediate (VI). Finally, the dithiocarbonate derivative (VI) is hydrolized by means of NaOH and then treated with HCl (1). Scheme 1.

Background

Pleuromutilin was first isolated in 1951 from *Pleurotus mutilus*, an edible mushroom. Nearly two decades later, this compound was discovered to have excellent activity against *Mycoplasma* spp. Tiamulin and valnemulin are semisynthetic derivatives of pleuromutilin employed for veterinary use, and a third analogue, azamulin, was studied as a potential antibiotic for use in humans. When the pleuromutilins were first investigated, most research was focused on the development of β-lactam, macrolide and quinolone antibacterial agents. However, more recently, due to the emergence of multidrug-resistant pathogens,

B. Boyd, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Retapamulin



efforts are being made to develop new classes of antimicrobials with novel modes of action and activity against resistant organisms. This strategy has led to the reassessment of previously discovered antibacterial agents that have not yet been used in humans. Pleuromutilins display a unique mode of action, inhibiting bacterial protein synthesis by specifically targeting the large subunit of the bacterial ribosome (3). Retapamulin (SB-275833) is a semisynthetic member of the pleuromutilin class of antibiotics, developed for the topical treatment of uncomplicated skin and skin structure infections (SSSIs) due to susceptible strains of *Staphylococcus aureus* or *Streptococcus pyogenes*, particularly impetigo (4-6).

Preclinical Pharmacology

In a recent study characterizing the interactions of retapamulin with bacterial ribosomes, results indicated that retapamulin is a selective and potent inhibitor of bacterial protein synthesis. This compound had IC_{50} values of 0.33 and > 100 μM in a bacterial coupled transcription-translation assay and a eukaryotic translation assay system, respectively. In addition, retapamulin showed extremely high binding affinity (K_d approx. 3 nM) for *Escherichia coli* and *S. aureus* ribosomes. The compound also potently inhibited bacterial ribosomal peptidyltransferase (IC_{50} = 26 nM). Overall, data from this study indicate that the retapamulin binding site on the 50S ribosomal subunit involves nucleotides in the region of the ribosomal P-site and peptidyltransferase center. Retapamulin inhibited fmet-tRNA binding to the P-site of *E. coli* ribosomes *in vitro* (IC_{50} = 29 nM), a finding which suggests that the compound may have an effect on translation initiation. Furthermore, retapamulin interacts with domain V of 23S rRNA in a manner that is different from the macrolides and ketolides (7).

The *in vitro* activity of retapamulin was examined using organisms isolated from SSSIs. The MIC_{90} values for retapamulin against nearly 4,000 clinical isolates of staphylococci, β-hemolytic streptococci (including *S. pyogenes* and *Streptococcus agalactiae*) and viridans streptococci were determined. The MIC_{90} values against clinical isolates of *S. aureus* were 0.12 μg/ml for retapamulin and 16, > 128, 32, 8-16, > 32, 2, > 32, 1, 2, 2-4, 4, 64 or more, 32 and 16-32 μg/ml, respectively, for amoxicillin/clavulanic acid, bacitracin, ceftriaxone, cephalothin, clindamycin, cloxacillin, erythromycin, fusidic acid, gentamicin, linezolid, mupirocin, neomycin, penicillin and tetracycline. Against isolates of coagulase-negative staphylococci, including *S. epidermidis*, the MIC_{90} values were 0.06-0.12, 8, > 128, 32-64, 4, > 32, 16, > 32, 4-8, 16, 2, > 256, 16-32, 16 and 32 μg/ml or more for the respective agents. Against clinical isolates of *S. pyogenes*, the MIC_{90} value for retapamulin was 0.03-0.06 μg/ml, as compared to MIC_{90} values of 0.12, 32-64, 0.06-0.12, 0.25, 0.12-0.25, 0.5, 2, 8, 16, 1, 0.5, 64, 0.03-0.06 and 16-32 μg/ml, respectively, for amoxicillin/clavulanic acid, bacitracin, ceftriaxone, cephalothin, clindamycin, cloxacillin, erythromycin, fusidic acid, gentamicin, linezolid, mupirocin, neomycin, penicillin and tetracycline. Similarly, for clinical isolates of *S. agalactiae*, the MIC_{90} values were 0.06 μg/ml for retapamulin and 0.25, 128, 0.12, 0.5,

4-32, 2, 8-32, 16, 32, 1, 1, 64 or more, 0.12 and > 32 μg/ml, respectively, for the other agents. Against strains of viridans streptococci, the MIC_{90} value for retapamulin was 0.25 μg/ml, as compared to 1, 128, 1, 1-2, 4-16, 8, 16-> 32, 32, 16, 1, 2, 64 or more, 1 and 32 μg/ml or more, respectively, for the comparators. Against macrolide-resistant strains of *S. pyogenes*, retapamulin showed an MIC_{90} value of 0.06 μg/ml, as compared to an MIC_{90} value of 0.03 μg/ml for macrolide-susceptible strains. Retapamulin retained its *in vitro* activity against strains resistant to methicillin, erythromycin, mupirocin or fusidic acid (8-13).

Retapamulin demonstrated excellent antibacterial activity against 392 clinical isolates of Gram-positive and Gram-negative organisms. In this study, retapamulin had MIC_{90} values of 0.125, 0.125, 0.125, 0.016, 0.125, 0.03, 0.125, 2 and 0.03 μg/ml, respectively, against *S. aureus* (100 isolates), *S. epidermidis* (40 isolates), *Staphylococcus saprophyticus* (28 isolates), *S. pyogenes* (101 isolates), *Streptococcus pneumoniae* (26 isolates), *S. agalactiae* (27 isolates), *Streptococcus viridans* (23 isolates), *Haemophilus influenzae* (27 isolates) and *Moraxella catarrhalis* (20 isolates). For comparison, mupirocin had MIC_{90} values of 0.5, > 16, 8, 0.5, 4, 1, 2, 0.125 and 2 μg/ml, respectively, against the same organisms; fusidic acid gave respective MIC_{90} values of 0.5, 0.25, 8, 16, 32, 16, 32, 16 and 0.06 μg/ml; bacitracin showed MIC_{90} values of 2 μg/ml for *S. pyogenes*, 4 μg/ml for *M. catarrhalis* and > 16 μg/ml for all other organisms tested; amoxicillin yielded MIC_{90} values of 64, 0.5, 0.5, 0.016 or less, 2, 0.06, 8, > 64 and 8 μg/ml against *S. aureus, S. epidermidis, S. saprophyticus, S. pyogenes, S. pneumoniae, S. agalactiae, S. viridans, H. influenzae* and *M. catarrhalis*, respectively; azithromycin gave respective MIC_{90} values of > 64, > 64, > 64, 4, > 8, 2, > 8, 2 and 0.03 μg/ml; levofloxacin had MIC_{90} values of 16, 8, 0.5, 2, 1, 1, 2, 0.016 and 0.03 μg/ml against the respective microorganisms; and cefaclor showed MIC_{90} values of > 64, 1, 4, 0.25, > 8, 2 > 8, > 16 and 2 μg/ml, respectively (14).

The *in vitro* activity of retapamulin was tested against 1,690 Gram-positive clinical isolates commonly associated with SSSIs collected between 1998 and 2004 in the U.S. and Europe. The MIC_{90} values for retapamulin were 0.25, 0.06, 0.12, 0.25, 0.5, 0.06, 128, 0.5 and 0.25 μg/ml, respectively, against *S. aureus* (500 isolates), *S. pyogenes* (500 isolates), *S. epidermidis* (100 isolates), *S. saprophyticus* (100 isolates), viridans streptococci (101 isolates), *S. agalactiae* (100 isolates), *Bacillus* spp. (102 isolates), *Corynebacterium* spp. (101 isolates) and *Micrococcus* spp. (86 isolates). Retapamulin exhibited a better profile of *in vitro* activity than bacitracin, cephalothin, ciprofloxacin, erythromycin, gentamicin, mupirocin, oxacillin and penicillin, and maintained good activity against methicillin-resistant, vancomycin-intermediate and vancomycin-resistant strains (MIC = 0.06-0.5 μg/ml) (15).

The *in vitro* activities of retapamulin, erythromycin, fusidic acid and mupirocin were determined against 503 isolates of *S. pyogenes*, 130 isolates of *S. agalactiae* and 105 isolates of viridans streptococci. The MIC_{90} values found for retapamulin were 0.03, 0.06 and 0.25 μg/ml, respectively, *vs.* respective values for erythromycin of 16, 16 and 128 μg/ml or more, for fusidic acid of 8, 16 and 32 μg/ml and for mupirocin of 0.12, 1 and 1 μg/ml (16).

The antibacterial activities of retapamulin and comparators were evaluated against a total of 604 recent clinical isolates of *S. aureus* (281 strains), coagulase-negative staphylococci (232 strains) and *S. pyogenes* (91 strains), including oxacillin-, mupirocin- and erythromycin-resistant strains. Retapamulin showed an MIC_{90} value of 0.12 μg/ml against all drug-resistant strains of *S. aureus* tested, as well as against wild-type susceptible *S. aureus*. For comparators, the MIC_{90} values against susceptible *S. aureus* isolates were 1, > 4, 0.25 or less, 0.12 or less, 0.5, 2, 0.5 and > 2 μg/ml, respectively, for tiamulin, bacitracin, cephalothin, clindamycin, gentamicin, linezolid, ofloxacin and penicillin. Against erythromycin-resistant strains of *S. aureus*, the MIC_{90} values for the respective agents were 1, > 4, > 32, > 100, 30, 2, > 30 and > 2 μg/ml. The MIC_{90} values against mupirocin-resistant *S. aureus* isolates were 1, > 4, > 32, > 100, 30, 2, > 30 and > 2 μg/ml for the respective comparators. Against oxacillin-resistant strains of *S. aureus*, the MIC_{90} values were 1, > 4, > 32, > 100, 30, 2, > 30 and > 2 μg/ml, respectively. The MIC_{90} value of retapamulin against coagulase-negative staphylococci was 0.06 μg/ml for both oxacillin- and mupirocin-resistant strains, as well as for wild-type susceptible isolates. The MIC_{90} values against susceptible coagulase-negative staphylococci isolates were 0.5, > 4, 0.25 or less, 0.12 or less, 0.25, 2, 0.5 and > 2 μg/ml, respectively, for tiamulin, bacitracin, cephalothin, clindamycin, gentamicin, linezolid, ofloxacin and penicillin. Against mupirocin-resistant strains of coagulase-negative staphylococci, the MIC_{90} values were 0.5, > 4, 2, > 100, 30, 1, > 30 and > 2 μg/ml for the respective agents. The MIC_{90} values against oxacillin-resistant coagulase-negative staphylococci were 0.5, > 4, 4, > 100, 30, 1, > 30 and > 2 μg/ml, respectively. Retapamulin gave an MIC_{90} value of 0.03 μg/ml or less against erythromycin-resistant *S. pyogenes*, as compared to MIC_{90} values of 0.25 or less, 2 or less, > 4, 0.25 or less, > 100, 8, 1, 1, 0.25 or less and 0.03 μg/ml or less, respectively, for tiamulin, mupirocin, bacitracin, cephalothin, clindamycin, gentamicin, linezolid, ofloxacin, oxacillin and penicillin (17).

Another recent study investigated the *in vitro* activity of retapamulin against 141 clinical isolates of *Propionibacterium* spp., including 7 multiresistant strains. Against 117 strains of *Propionibacterium acnes*, the MIC_{90} values were 0.25, 0.25, 0.06, 1 and 1 μg/ml for retapamulin, clindamycin, erythromycin, tetracycline and trimethoprim/sulfamethoxazole, respectively. In addition, retapamulin had an MIC of 1 μg/ml or less against *P. acnes* strains resistant to comparator drugs, including 5 strains with erythromycin MIC values of > 128 μg/ml, 3 strains with tetracycline MIC values of 8 μg/ml or more and 3 strains with clindamycin MIC values of 4 μg/ml or more. When tested against 12 strains of

Propionibacterium avidum, retapamulin gave an MIC_{90} value of 0.015 μg/ml, as compared to values of 0.06, 0.125, 4 and > 8 μg/ml, respectively, for clindamycin, erythromycin, tetracycline and trimethoprim/sulfamethoxazole. The MIC_{90} values against *Propionibacterium granulosum* were 0.015 or less, 0.03, 0.125, 2 and > 8 μg/ml for retapamulin, clindamycin, erythromycin, tetracycline and trimethoprim/sulfamethoxazole, respectively (18, 19).

The *in vitro* activity of retapamulin was determined against 232 isolates of anaerobic organisms collected in 2003 and 2004 from human skin samples. Against 25 strains of *Bacteroides fragilis*, the MIC_{90} values were 64, > 64, 16, 64, 4, > 256 and 4 μg/ml, respectively, for retapamulin, amoxicillin, amoxicillin/clavulanic acid, ceftriaxone, imipenem, clindamycin and metronidazole. The MIC_{90} values against 10 strains of *Bacteroides thetaiotaomicron* were > 64, > 64, 2, > 128, 2, > 256 and 2 μg/ml for the respective agents. Against 17 strains of other species in the *B. fragilis* group, the MIC_{90} values were 32, > 64, 16, > 128, 1, > 256 and 4 μg/ml, respectively. When tested against 33 strains of *Prevotella* spp., the MIC_{90} value of retapamulin was 0.03 μg/ml, as compared to 0.125, 0.06 or less, 2, 0.03 or less, 0.06 or less and 0.5 μg/ml, respectively, for amoxicillin, amoxicillin/clavulanic acid, ceftriaxone, imipenem, clindamycin and metronidazole. Against 29 strains of *Porphyromonas* spp., the MIC_{90} values were 0.015, 0.06, 0.06, 0.03, 0.03, 0.06 and 0.06 μg/ml or less, respectively, for retapamulin, amoxicillin, amoxicillin/clavulanic acid, ceftriaxone, imipenem, clindamycin and metronidazole, and the MIC_{90} values determined against 25 strains of *Fusobacterium* spp. were 2, 16, 0.5, 128, 0.5, 4 and 0.5 μg/ml for the respective agents. Testing against 14 strains of *Clostridium perfringens* yielded MIC_{90} values of 1, 0.06 or less, 0.06 or less, 4, 0.5, 0.5 and 1 μg/ml, respectively, and the corresponding MIC_{90} values against 15 strains of other *Clostridium* spp. were 64, 2, 2, 64, 2, 256 and 0.5 μg/ml. Against 25 strains of *P. acnes*, the respective agents yielded MIC_{90} values of 0.25, 0.25, 0.25, 0.5, 0.125, 0.25 and > 64 μg/ml. Retapamulin also displayed good activity against Gram-positive anaerobic cocci, with an MIC_{90} of 1 μg/ml compared to 0.25, 0.25, 8, 0.25, 32 and 2 μg/ml, respectively, for amoxicillin, amoxicillin/clavulanic acid, ceftriaxone, imipenem, clindamycin and metronidazole (20).

Another study involving 226 strains of Gram-negative and Gram-positive anaerobic bacteria collected from human skin samples compared the *in vitro* activity of retapamulin with clindamycin, metronidazole, mupirocin, neomycin and tetracycline. The MIC_{90} values were 64, > 128, 2, > 128, > 128 and 128 μg/ml, respectively, against 35 strains belonging to the *B. fragilis* species group, 4, 0.5, 8, 1, 4 and 16 μg/ml, respectively, against 23 *Bacteroides* spp. strains, 1, 0.125, 1, 0.06, > 128 and 2 μg/ml, respectively, against 26 strains of *Fusobacterium* spp., 0.03, > 128, 0.25, > 128, > 128 and 16 μg/ml, respectively, against 25 strains of *Porphyromonas* spp., 0.06, 0.06, 4, > 128, > 128 and 32 μg/ml, respectively, against 28 strains of *Prevotella* spp., 16, 4, 32, > 128, > 128 and 16 μg/ml, respectively, against 31 strains of *Clostridium* spp., 0.03, 0.06, > 128, > 128, 8 and 0.5 μg/ml, respectively, against 30 strains of *P. acnes*, and 1, > 128, 2, > 128, > 128 and 64 μg/ml, respectively, against 28 strains of anaerobic Gram-positive cocci. Overall, the MIC_{90} values against all 226 anaerobic isolates studied were 2 μg/ml for retapamulin and clindamycin, > 128 μg/ml for metronidazole, mupirocin and neomycin, and 32 μg/ml for tetracycline (21).

The *in vitro* activities of retapamulin, mupirocin and moxifloxacin were tested against 974 mostly recent bacterial isolates. The MIC_{90} values determined against all *Staphylococcus* strains combined (n=331) were 0.12, 1 and > 0.5 μg/ml for retapamulin, mupirocin and moxifloxacin, respectively. Among the 102 strains of coagulase-negative staphylococci tested, the MIC_{90} values were 0.12, > 32 and > 0.5 μg/ml for retapamulin, mupirocin and moxifloxacin, respectively, with similar levels of activity being seen against oxacillin-resistant and -susceptible strains. When tested against 229 strains of *S. aureus*, the agents yielded MIC_{90} values of 0.12, 0.5 and > 0.5 μg/ml, respectively. Among the subset of 109 oxacillin-resistant strains of *S. aureus*, the MIC_{90} values were 0.12, 2 and > 0.5 μg/ml, respectively, and among the 20 vancomycin-intermediate strains of *S. aureus*, the respective MIC_{90} values were 0.12, 1 and > 0.5 μg/ml. Testing against a total of 390 strains of streptococci revealed MIC_{90} values of 0.06, 2 and 0.25 μg/ml for retapamulin, mupirocin and moxifloxacin, respectively. The MIC_{90} values against all strains of *Enterococcus* spp. combined (n=102) were 128, > 32 and > 0.5 μg/ml for retapamulin, mupirocin and moxifloxacin, respectively. Retapamulin demonstrated little activity against Gram-negative bacilli (n=151), with an MIC_{90} of > 512 μg/ml; the corresponding MIC_{90} values for mupirocin and moxifloxacin were > 32 and > 0.5 μg/ml (22).

Retapamulin has a low potential to select for resistant mutants in *S. pyogenes*, according to a study that assessed the resistance generated against a number of antibacterial agents in multiple- and single-passage testing. In multiple-passage studies, retapamulin exhibited lower MIC values against *S. pyogenes* than the other agents tested (*i.e.*, mupirocin, cefalexin, erythromycin, linezolid, vancomycin and quinupristin/dalfopristin). In 3 of the 10 isolates tested, retapamulin selected clones after 26-48 days. The MIC values were 0.125-0.25 μg/ml for these selected clones, as compared to MIC values of 0.016-0.03 μg/ml for the parents (representing an 8-fold increase). Even prolonged 50-day incubation with retapamulin did not raise the MIC values of these clones. In the single-passage studies, the resistance frequency against *S. pyogenes* was found to be lower for retapamulin that for the other agents tested. One multiple-passage clone had an L3 mutation (N149K) and was associated with an 8-fold increase in retapamulin MIC after 48 days; however, none of the 7 randomly selected single-passage clones exhibited altered L3 protein (23).

Another study determined the potential of retapamulin to select for resistant mutants in 12 strains of *S. aureus*,

including 1 mupirocin-resistant and 1 fusidic acid-resistant strain, as well as 2 vancomycin-intermediate and 3 vancomycin-resistant strains. Mupirocin, fusidic acid, cefalexin, erythromycin, linezolid, vancomycin and quinupristin/dalfopristin were used as comparators. After 14-20 days, retapamulin yielded resistant clones in all 12 strains, although retapamulin had the lowest MIC values of all the agents tested in the multiple-step resistance study. The MIC values for retapamulin-selected resistant clones were 8-32-fold higher that those for parents, but none of the MICs reached values above 2 μg/ml. In single-passage resistance studies, the frequency of spontaneous resistance to retapamulin was lower than for all other agents tested except linezolid (24).

In a study to determine the postantibiotic effects (PAEs) of retapamulin and mupirocin, clinical isolates of *S. aureus, S. pyogenes, S. pneumoniae* and *H. influenzae* were incubated in the presence of 4 x MIC concentrations of each of the drugs for 2 h. The PAEs against *S. aureus* (3 strains) were found to be 3.1-3.4 h for retapamulin (MIC = 0.06-0.125 μg/ml) and 2.2-2.9 h for mupirocin (MIC = 0.25-0.50 μg/ml). When tested against *S. pyogenes* (4 strains), retapamulin showed a PAE of 3.5-4.2 h (MIC = 0.008-0.016 μg/ml) and mupirocin had a PAE of 2.2-3.2 h (MIC = 0.06-0.125 μg/ml). The PAEs against *S. pneumoniae* (2 strains) were 3.7-4.7 h for retapamulin (MIC = 0.03-0.06 μg/ml) and 1.3-2.2 h for mupirocin (MIC = 0.125-2.00 μg/ml). Finally, the results of testing against *H. influenzae* (2 strains) yielded PAEs of 3.3-5.2 h for retapamulin (MIC = 0.25-1.00 μg/ml) and 2.1-3.5 h for mupirocin (MIC = 0.06 μg/ml) (25).

Retapamulin showed excellent *in vitro* activity against 109 methicillin-resistant *S. aureus* isolates obtained from skin specimens collected from patients enrolled in phase III clinical trials. Results from this study demonstrated that retapamulin was active against all methicillin-resistant *S. aureus* isolates tested, independent of SCC*mec* (staphylococcal casette chromosome *mec*) type or the presence of PVL (Panton-Valentine leukocidin) genes. For 67 PVL-positive, SCC*mec* type IV isolates, the retapamulin MIC_{50} and MIC_{90} values were both 0.12 μg/ml. When tested against 14 PVL-negative, SCC*mec* type IV isolates, retapamulin yielded MIC_{50} and MIC_{90} values of 0.06 and 0.12 μg/ml, respectively. Against 28 PVL-negative, SCC*mec* type II, III or IIIA isolates, the retapamulin MIC_{50} and MIC_{90} values were 0.06 and 0.12 μg/ml, respectively (26).

An *in vivo* study tested the efficacy of topical retapamulin against resistant strains of *S. aureus* in a murine wound infection model. The antibacterial efficacy of retapamulin (1% w/w b.i.d.) was compared to that of mupirocin (2% w/w t.i.d.) and fusidic acid (2% w/w t.i.d.). The retapamulin MIC values for the *S. aureus* strains tested were 0.12 μg/ml for F306 (methicillin- and azithromycin-resistant) and X32717 (methicillin-, mupirocin-, azithromycin- and levofloxacin-resistant), 0.06 μg/ml for T63256 (methicillin-, mupirocin-, azithromycin- and levofloxacin-resistant) and 1080 (mupirocin- and azithromycin-resistant), and 0.03 μg/ml for S5112 (mupirocin-, azithromycin- and levofloxacin-resistant). Retapamulin also displayed equivalent or superior efficacy to the other agents in reducing bacterial counts in this infection model (27).

Drug Interactions

A randomized, open-label, crossover phase I study assessed the effects of ketoconazole on the pharmacokinetics of retapamulin in 28 healthy adult males. Volunteers were exposed for 24 h to 1% retapamulin ointment applied postabrasion to 50 cm^2 of skin either alone or on day 4 of oral ketoconazole treatment (200 mg b.i.d.). The mean retapamulin $AUC_{0\text{-}24h}$ was 98.73 ng.h/ml in subjects receiving ketoconazole and 54.96 ng.h/ml in volunteers not receiving ketoconazole. The mean retapamulin C_{max} was 7.63 ng/ml in subjects receiving ketoconazole and 4.27 ng/ml in those not receiving ketoconazole. Oral ketoconazole thus induced an 81% increase in both the $AUC_{0\text{-}24h}$ and C_{max} of retapamulin, although it did not affect the t_{max}. Only infrequent and mild adverse events were observed. One subject withdrew early due to elevated serum creatinine levels during ketoconazole treatment and another subject withdrew due to a positive urine drug screen. No relationship was noted between cardiac Q-T interval and retapamulin plasma concentrations. The increased systemic retapamulin exposure observed with the co-administration of oral ketoconazole was not considered to be clinically relevant. Based on these results, the authors concluded that oral cytochrome P-450 CYP3A4 and P-glycoprotein inhibitors such as ketoconazole can be safely co-administered with topical retapamulin without the need for dose adjustment (28).

Clinical Studies

Retapamulin ointment is being tested in two phase III clinical studies for the topical treatment of impetigo (4-6).

Source

GlaxoSmithKline plc. (GB).

References

1. Breen, G.F., Forth, M.A., Kopelman, S.S.H., Muller, F.X., Sanderson, F.D. (GlaxoSmithKline plc). *Novel process, salts, compositions and use*. WO 2005023257.

2. Berry, V., Dabbs, S., Frydrych, C.H., Hunt, E., Woodnutt, G., Sanderson, F.D. (GlaxoSmithKline plc; GlaxoSmithKline Inc.). *Pleuromutilin derivatives as antimicrobials*. EP 1028961, EP 1452534, JP 2001521033, US 6281226, WO 1999021855.

3. Hunt, E. *Pleuromutilin antibiotics*. Drugs Fut 2000, 25: 1163-8.

4. *First in new class of antibacterials demonstrates promising activity against pathogens commonly found in skin infections*. GlaxoSmithKline Press Release December 19, 2005.

5. *Topical SB-275833 ointment for the treatment of impetigo (NCT00133874)*. ClinicalTrials.gov Web Site 2005, December 8.

6. *Treatment of impetigo with topical SB-275833 ointment versus topical placebo ointment (NCT00133848)*. ClinicalTrials.gov Web Site 2005, December 8.

7. Yan, K., Voigt, C., Madden, L., Choudhry, A., Copeland, R.A., Gontarek, R.R. *Characterization of the interactions of retapamulin with bacterial ribosomes*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2051.

8. Bouchillon, S., Hoban, D., Johnson, B., Jordan, A., Scangarella, N., Shawar, R., Johnson, J. *Retapamulin (SB-275833), a novel pleuromutilin – A multi-center global surveillance of activity against 3,797 beta and alpha hemolytic streptococci isolated from skin and skin structure infections (SSSIs)*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2061.

9. Johnson, B., Jordan, A., Bouchillon, S., Hoban, D., Scangarella, N., Shawar, R., Johnson, J. *In vitro activity of retapamulin (SB-275833), a novel topical antimicrobial, against 3721 Gram-positive isolates associated with skin and skin structure infections (SSSIs) from 17 sites in North America*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2050.

10. Stevens, T., Johnson, B., Bouchillon, S., Hoban, D., Scangarella, N., Shawar, R., Johnson, J., Badal, R. *A multi-center global surveillance study of the in vitro activity of retapamulin (SB-275833), a novel topical pleuromutilin, against 2950 clinical isolates of S. aureus and coagulase-negative staphylococci from uncomplicated skin and skin structure infections (SSSIs)*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2062.

11. Bouchillon, S., Johnson, B., Stevens, T., Hoban, D.J., Scangarella, N.E., Shawar, R.M., Johnson, J.L. *Retapamulin (SB-275833), a novel topical pleuromutilin, is active in vitro against community-associated methicillin- and mupirocin-resistant S. aureus isolates from uncomplicated skin and skin structure infections (SSSIs)*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2059.

12. Bouchillon, S., Johnson, B., Stevens, T., Hoban, D., Scangarella, N., Shawar, R., Johnson, J.L. *Recent surveillance study of 2,901 Gram-positive isolates associated with skin and skin structure infections (SSSIs) in the United States demonstrates excellent activity of retapamulin (SB275833), a novel topical antimicrobial*. 43rd Annu Meet Infect Dis Soc Am (IDSA) (Oct 6-9, San Francisco) 2005, Abst 536.

13. Bouchillon, S.K., Johnson, B.M., Stevens, T.M., Hoban, D.J., Scangarella, N.E., Shawar, R.M, Johnson, J.L. *Methicillin- and mupirocin-resistance in community-associated S. aureus obtained from uncomplicated skin and skin structure infections (SSSIs) in the United States in 2004-2005: Retapamulin surveillance study*. 43rd Annu Meet Infect Dis Soc Am (IDSA) (Oct 6-9, San Francisco) 2005, Abst 507.

14. McCloskey, L., Zonis, R., Broskey, J., Biswas, S., Pizzollo, J., Jakielaszek, C., Payne, D., Rittenhouse, S. *In vitro spectrum of retapamulin (RE) activity against organisms associated with skin structure and community acquired infections*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2055.

15. Draghi, D., Scangarella, N., Shawar, R., Sahm, D. *In vitro activity of retapamulin and comparators against 1690 recent Gram-positive clinical isolates*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2052.

16. Felmingham, D., Williams, L.J., Northwood J.G.E., Crowhurst, N.A. *In vitro activity of retapamulin, a novel pleuromutilin, against Streptococcus pyogenes, S. agalactiae and "viridans" Streptococcus spp. isolates from 26 centres in 14 European countries*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2056.

17. Jones, R.N., Fritsche, T.R., Sader, H.S., Biedenbach, D.J. *Comparative antimicrobial activity and spectrum of retapamulin (RE) against drug-resistant organisms*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2053.

18. Goldstein, E.J.C., Citron, D.M., Vreni Merriam, C., Warren, Y.A., Tyrrell, K.L., Fernandez, H.T. *Comparative in vitro activities of retapamulin (SB-275833) against 141 clinical isolates of Propionibacterium spp., including 117 P. acnes isolates*. Antimicrob Agents Chemother 2006, 50: 379-81.

19. Goldstein, E.J.C., Citron, D.M. *Comparative in vitro activity of retapamulin against 141 clinical isolates of Propionibacterium spp. including 117 isolates of P. acnes*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2057.

20. Dubreuil, L.J., Calvet, L., Odou, M.F., Muller, C. *Antianaerobic activity of retapamulin (RE), a new pleuromutilin antibiotic*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2058.

21. Molitoris, D.R., Finegold, S.M., Bolanos, M. *In vitro activity of retapamulin and five comparator agents against 226 anaerobic bacterial isolates*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2060.

22. Brown, S.D., Traczewski, M.M. *Retapamulin (RE): In vitro potency, spectrum of activity, MIC and disk breakpoints*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2065.

23. Clark, C., Kosowska-Shick, K., Credito, K., Appelbaum, P.C. *Low potential of retapamulin to select for resistant mutants in Streptococcus pyogenes*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2069.

24. Clark, C., Kosowska-Shick, K., Credito, K., Appelbaum, P. *Low potential of retapamulin to select for resistant mutants in S. aureus*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2068.

25. Moore, T., Broskey, J., Pizzollo, J., McCloskey, L., Rittenhouse, S. *Post-antibiotic effects of retapamulin and mupirocin against S. aureus, S. pyogenes, S. pneumoniae and H. influenzae*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2067.

26. West, J., Ray, R., Scangarella, N., Shawar, R. *Antibacterial activity of retapamulin against 109 MRSA skin infection isolates with characterized SCCmec and PVL genotypes recovered from phase III clinical trials*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2054.

27. Singley, C., Hoover J., Page, R., Payne, D., Rittenhouse, S. *Efficacy of retapamulin (RE) administered topically against*

methicillin, mupirocin and multi-drug resistant strains of S. aureus in a murine wound infection model. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2070.

28. Min, S.S., Zhu, J., Kurtinecz, M., Phillips, J., Wallace, D. *Pharmacokinetic (PK) interaction between topical application of retapamulin (RE) ointment, 1%, and oral ketoconazole*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2071.

Additional References

Ross, J.E., Jones, R.N. *Quality control guidelines for susceptibility testing of retapamulin (SB-275833) by reference and standardized methods*. J Clin Microbiol 2005, 43: 6212-3.

Koeth, L.M., DiFranco, J.M. *The effect of testing parameter variations on the in vitro activity of retapamulin and mupirocin*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2064.

Pankuch, G., Lin, G., Jacobs, M.R., Appelbaum, P.C. *Comparison of 4 methods for susceptibility testing of retapamulin against Staphylococcus aureus and Streptococcus pyogenes*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2063.

Ross, J.E., Sader, H.S., Fritsche, T.R., Jones, R.N. *Quality control guidelines for testing retapamulin by CLSI broth microdilution and disk diffusion methods*. 45th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Dec 16-19, Washington DC) 2005, Abst F-2066.