

Isis Pharmaceuticals, Inc.

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Re: ACHN-490 against pneumonia

Chicago, Sept 18, 2011 meeting of ICAAC, conference on anti-microbial agents and chemotherapy (if I remember correctly).

In order to treat bacterial pneumonia, antibiotics must maintain antimicrobial activity in the presence of pulmonary surfactant, a complex mixture of lipids and proteins. It has previously been reported that the activity of daptomycin, an antibiotic with Gram-positive activity, was inhibited in the presence of surfactant. Plazomicin (previously ACHN-490), a broad spectrum aminoglycoside, is being developed to treat resistant bacterial pathogens. The in vitro activity of plazomicin and 6 comparator antibiotics was examined in the presence of varying levels of surfactant. Methods: MICs were determined for plazomicin, amikacin, gentamicin, tobramycin, cefepime, and levofloxacin against 10 Gram-positive (Staphylococcus aureus) and 10 Gram-negative (5 each of Pseudomonas aeruginosa and Klebsiella pneumoniae) strains in the presence of 1%, 5%, and 10% bovine-derived lung surfactant, beractant (Abbott). Daptomycin and vancomycin were tested against S. aureus strains. Results: The activity of plazomicin and comparator aminoglycosides against the 20 strains tested was not measurably affected by the addition of up to 10% surfactant (fold changes in MIC upon surfactant addition ranged from 0.25 to 4). The remaining antibiotics tested showed no consistent changes in potency with addition of surfactant causing 0.5- to 2-fold changes in MIC. In contrast, the activity of daptomycin against the S. aureus strains decreased from 16- to 32-fold in the presence of 1% surfactant and decreased at least 32-fold with 5% or 10% surfactant. Conclusions: There was no surfactant-dependent decrease in plazomicin activity when either Gram-positive or Gram-negative bacteria were tested. With the exception of daptomycin, the activity of the comparator antibiotics was similarly unaffected by the presence of this surfactant.

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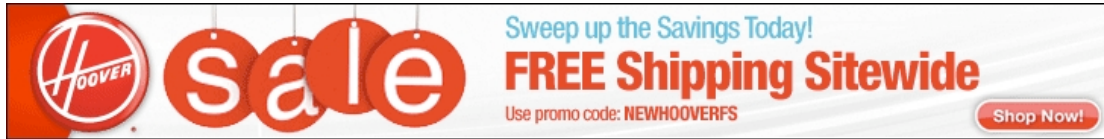
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