Information for Healthcare Professionals

Colistimethate
(marketed as Coly-Mycin M and generic products)

FDA ALERT [6/28/2007]: FDA is investigating the possible connection between the use of a liquid solution of colistimethate that was premixed for inhalation with a nebulizer and the death of a patient with cystic fibrosis (CF). The drug was prepared by a pharmacy and dispensed as prescribed in premixed unit dose ready-to-use vials. Colistimethate is used to treat *Pseudomonas aeruginosa* infections in the respiratory tract of patients with CF. Colistimethate is FDA approved for intravenous or intramuscular injection; it is not FDA approved for use as a liquid to be inhaled via nebulizer. However, in treating CF patients with Pseudomonas infections, colistimethate is often mixed with sterile water to form a solution just prior to inhalation via nebulizer. After mixing with sterile water and a buffer, colistimethate undergoes spontaneous hydrolysis to the bioactive form colistin. A component of colistin, polymyxin E1, is toxic to lung tissue. Premixing colistimethate into an aqueous solution and storing it for longer than 24 hours results in increased concentrations of colistin in solution, increasing the potential for lung toxicity.

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging drug safety issue. Nor does it mean that FDA is advising practitioners to discontinue prescribing the product. FDA is considering, but has not reached a conclusion about, whether this information warrants any regulatory action. FDA intends to provide updated information when it becomes available.

To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Recommendations and Considerations

Colistimethate is a parenteral antibiotic that is FDA approved for intramuscular or intravenous injection for the treatment of acute or chronic infections due to sensitive strains of certain Gram-negative bacilli, particularly sensitive strains of *Pseudomonas aeruginosa*. It is not FDA approved for use as a liquid to be inhaled via nebulizer. Infections with *P. aeruginosa* are a significant problem for patients with CF and for patients with neutropenia, and/or immune system compromise.

Information for Health Care Providers

- Health care providers who choose to prescribe Colistimethate for inhalation should be familiar with the chemistry of this product and understand that once Colistimethate is mixed with water and buffer, it undergoes spontaneous hydrolysis to the active form, colistin. A component of colistin, namely polymyxin E1, has been shown to cause pulmonary inflammatory reactions in animals and may also be contributing to the adverse effects in humans.
- To avoid this toxicity, this product should be administered promptly after it is mixed.

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Information for the Patient

- Patients should be advised not to use any pre-mixed, ready-to-use, liquid forms of Colistimethate prepared by a pharmacy for use in a nebulizer to deliver treatment directly to the lungs.
- Patients should be advised that the pre-mixed, ready-to-use, liquid form of Colistimethate breaks down to the active drug colistin. Colistin is a mixture of two components; one of those components may injure their lungs.
- Patients should be advised to discard any unused vials of pre-mixed, ready-to-use, liquid forms of Colistimethate.

Data Summary

Colistimethate is an inactive pro-drug of the bioactive form colistin. In aqueous solution, colistimethate undergoes spontaneous hydrolysis to form colistin. Colistin is a complex bioactive antimicrobial mixture with two active components, colistin A (polymyxin E1) and colistin B (polymyxin E2). In animal studies, polymyxin E1 has been shown to cause localized inflammation of the airway epithelia and eosinophilic infiltration.

In April 2007, a patient with CF had a home nebulizer treatment with a premixed liquid form of ready-to-use colistimethate. The premixed colistimethate had been supplied by a pharmacy. Within hours, the patient developed respiratory distress that progressed over several days to acute respiratory failure. The patient had copious amounts of thin pink pulmonary secretions and was admitted to intensive care. Bronchoscopy revealed clear central airways and no unusual pathogens. Pulmonary computerized tomography scan findings showed ground glass infiltrates, consistent with acute respiratory distress syndrome. The patient expired of multi-organ system failure about 19 days later.

FDA is currently investigating this report, and the pharmacy that prepared the patient's pre-mixed liquid form of ready-to-use Colistimethate and will update this information sheet when more is known.