



National Institute of Allergy and Infectious Diseases  
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

## Cholera

### A Possible New Drug to Treat Acute Diarrhea from Cholera and Other Conditions: Crofelemer

From deadly cholera epidemics to persistent, low-grade disease that causes malnutrition and reduced productivity, diarrhea can be devastating, particularly among infants, children and people infected with HIV. Until recently, antimicrobial drugs have been the key treatment for diarrhea. Yet, with the emergence of drug resistance and the untreatable infections that result, the search has been on for vaccines and new therapeutics to stifle diarrhea.

In February 2011, researchers completed a human clinical trial of the investigational anti-diarrheal drug crofelemer. The latest in a series of successful trials involving the drug, this study found that compared to a placebo, crofelemer treatment successfully reduced acute watery diarrhea in adults. Early development and testing studies of the drug by the San Francisco-based company Napo Pharmaceuticals, Inc., were supported by NIAID.

#### Early Trials Find Effectiveness against Cholera-induced Diarrhea

From 2006 to 2007, Napo received NIAID funding to study crofelemer, which restores the balance of fluid and electrolytes in the gastrointestinal tract. Crofelemer is derived from the sap of the *Croton lechleri* tree (also known as *Sangre de drago* or Dragon's Blood), found in the Northwest Amazon basin of South America. Historically, *Croton lechleri* sap has been used by indigenous groups in South America to treat diarrhea.



Adult cholera patient with severe dehydration  
Credit: CDC

When the NIAID-funded studies began, Napo scientists anticipated that the drug would be effective against cholera-induced diarrhea because the product had performed well in animal studies. As hoped, crofelemer safely reduced severe watery diarrhea in humans suffering from cholera and balanced the fluid and electrolyte levels in both laboratory mice and human subjects. Building on that success, Napo began testing how well it would reduce diarrhea caused by other gastrointestinal illnesses.

Researchers initially tested the drug in orally administered bead and tablet formulations. However, they found that these formulations released the drug in the stomach, too early in the digestive process for it to be effective. For the drug to be a useful treatment for watery diarrhea, Napo evaluated the use of crofelemer as a new coated tablet that released the drug later in the digestive process, in the intestinal tract, where it could effectively reduce diarrhea.

#### Potential Treatment for Diarrhea Related to HIV, Other Causes

In November 2010, Napo announced the completion of a Phase III clinical trial of crofelemer in HIV-infected patients receiving antiretroviral therapy, finding the drug to be an effective treatment for chronic diarrhea. HIV patients taking life-saving antiretroviral medicines to control the virus frequently experience diarrhea, causing

many patients to stop taking their HIV medicines, which can harm the patient and lead to the emergence of drug-resistant strains of HIV. By reducing the incidence of diarrhea associated with antiretroviral therapy, the researchers expect that patients with HIV will be more likely to stick to their treatment regimen.

In February 2011, Glenmark Pharmaceuticals, based in India, completed a Phase II trial comparing crofelemer to placebo in adults with acute watery diarrhea. They found that compared to placebo, three days of crofelemer treatment significantly reduced diarrhea over the following 30 days. Additionally, the highest dosage level, 500 mg per day, was significantly more effective than the lowest dose studied, 125 mg per day.

### **Next Steps**

To date, crofelemer has been found to be safe, with no serious side effects or interactions with other drugs. Because diarrheal diseases are so prevalent in developing countries, crofelemer is being considered for further study and use in up to 140 countries in the developing world. Additional steps include testing the drug in children and as a treatment for irritable bowel syndrome.

### **References:**

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