

Additional Considerations in the Use of Opioids for Cough

September 11, 2017

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Outline

- Principles of Treatment of Acute Cough
- Treatment Guidelines
- Global Regulatory Actions
- Current Pediatric Labeling
- PREA Requirements
- Summary of the Expert Roundtable Meeting

Principles of Treatment of Acute Cough

- Cough in pediatric patients is typically a non-serious condition which is self-limiting, commonly secondary to infection.
- Symptomatic treatment of cough in certain conditions may be detrimental.
- When a specific etiology of cough can be identified in a pediatric patient, therapy should be directed at treating the underlying condition.
- There have been changes in the recommendations for the management of cough in children in the last decade.

Treatment Guidelines

Based on their review of the relevant literature and with input from experts in the field, the World Health Organization and other leading pediatric and pulmonary health organizations including the American Academy of Pediatrics and the American College of Chest Physicians recommend against the symptomatic treatment of cough in the pediatric population.

Treatment Guidelines

American Academy of Pediatrics (AAP)

- The AAP found no adequate and well-controlled scientific studies that support the efficacy and safety of any cough suppressant in children, including opioid-containing products.
- The AAP concluded that “education of patients and parents about the lack of proven antitussive effects and the potential risks of [cough suppressants] is needed.”

Treatment Guidelines

American College of Chest Physicians (ACCP)

- Recommended against the use of cough suppressants and “other OTC cough medications”, especially in young children, due to the possibility of significant morbidity and mortality.

World Health Organization (WHO)

- Recommended against the use of codeine for the treatment of cough in young children

Global Regulatory Actions

European Medicines Agency (EMA)

- Contraindicated the use of codeine in patients less than 12 years and recommended against the use of codeine in patients 12 to 18 years with breathing problems.

Health Canada

- Cautioned against the use of OTC cough and cold medications in pediatric patients less than 6 years.
- Recommended against the use of hydrocodone in pediatric patients less than 6 years and the use of codeine in patients less than 12 years
- Neither codeine nor hydrocodone should be used in patients with breathing problems

Current Pediatric Labeling

Prescription Codeine Products

- Labeling for all products has:
 - Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine
 - Contraindication for postoperative management in children <18 years post tonsillectomy & adenoidectomy (T& A)
 - Contraindication in children <12 years
- Labeling for older products have dosing information for children 12 years and older
- Newer codeine antitussives are not indicated for patients <18 years awaiting completion of studies under the Pediatric Research Equity Act (PREA)

Current Pediatric Labeling

Prescription Hydrocodone products

- Hydrocodone bitartrate and homatropine methylbromide and Hydrocodone polistirex and chlorpheniramine polistirex
 - dosing information for 6 years and older
 - warning to use with caution in pediatric patients ≥ 6 years.
- Hydrocodone bitartrate and homatropine methylbromide
 - warning for fatal respiratory depression in children < 6 years of age.
- Hydrocodone polistirex and chlorpheniramine polistirex
 - contraindicated in children < 6 years
- All other hydrocodone antitussive products are not indicated for use in patients < 18 years

Pediatric Study Requirements

- Currently, pediatric studies for newly submitted prescription opioid cough products are required to conduct pediatric studies under the Pediatric Research Equity Act (PREA).
- PREA is triggered for any application for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration.
- Combination products with codeine and hydrocodone are considered new active ingredients and thus PREA is triggered.

Pediatric Study Requirements

- The required pediatric studies generally consist of information to support labeling in pediatric patients 6 to 17 years. The studies include:
 - A single dose PK study to establish pediatric dosing
 - A large safety study to provide sufficient safety information
- Efficacy is based upon the established efficacy in the OTC monograph or previously approved products.
- Based on the outcome of this Pediatric Advisory Committee, these requirements may change.



Expert Roundtable Meeting

On April 27, 2017, FDA held a roundtable meeting of invited experts to discuss the experience of health care professionals with the use of cough suppressants in children (less than 18 years of age), particularly opioid antitussive products.

The participants included representatives of professional organizations involved in the treatment of pediatric patients with cough.

The discussion of the experts during the roundtable meeting helped to frame the questions for this Pediatric Advisory Committee.

Expert Roundtable Meeting

The experts stated that in their clinical experience:

- The use of cough suppressants depends on the clinical situation, but should not be used unless the cough is causing clinical consequences.
- Identifying and treating the underlying cause of cough is important
- A clear role for the use of hydrocodone or codeine in the treatment of acute cough in pediatric patients was not obvious