

Food and Drug Administration
Center for Drug Evaluation and Research

**Summary Minutes of the Joint Pulmonary-Allergy Drugs Advisory Committee and
Drug Safety and Risk Management Advisory Committee Meeting**

December 10, 2015

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed the safety of codeine in children 18 years of age and younger. Codeine (most often in combination with acetaminophen) is used for the treatment of pain in children; however, it is contraindicated for the management of pain after tonsillectomy and/or adenoidectomy.

Codeine (in combination with other medicines) is used for the relief of cough associated with upper respiratory allergies or the common cold in children. Codeine is available by prescription and also through the over-the-counter (OTC) Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341.14, 21 CFR 341.74, and 21 CFR 341.90).

The focus of the meeting was on the risk of serious adverse events, such as respiratory depression and death, including reports in children who are CYP2D6 ultra-rapid metabolizers. The committees discussed whether the use of codeine in children should be restricted further beyond the current contraindication described previously and whether codeine should be available through the OTC Drug Monograph.

These summary minutes for the December 10, 2015 joint meeting of the Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on January 11, 2016.

I certify that I attended the December 10, 2015 joint meeting of the Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cindy Hong, PharmD
Designated Federal Officer
Pulmonary-Allergy Drugs
Advisory Committee (PADAC)

_____/s/_____
Dennis Ownby, MD
Chairperson, PADAC

December 10, 2015

Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

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December 10, 2015**

The following is the final report of the joint meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) held on December 10, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Pulmonary, Allergy, and Rheumatology Products and the Office of Surveillance and Epidemiology, and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm433815.htm> and
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm433818.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 10, 2015 from 8:00 a.m. to 4:00 p.m. at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA. The meeting was called to order by Dennis Ownby, MD (Chairperson). The conflict of interest statement was read into the record by Cindy Hong, PharmD (Designated Federal Officer). There were approximately 90 people in attendance. There were three (3) Open Public Hearing speakers.

Issue: The committee discussed the safety of codeine in children 18 years of age and younger. Codeine (most often in combination with acetaminophen) is used for the treatment of pain in children; however, it is contraindicated for the management of pain after tonsillectomy and/or adenoidectomy. Codeine (in combination with other medicines) is used for the relief of cough associated with upper respiratory allergies or the common cold in children.

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Attendance:

PADAC Members Present (Voting): John E. Connett, PhD; Steve N. Georas, MD; Mitchell Grayson, MD; Michelle Harkins, MD, FCCP; Francis X. McCormack, MD; Elaine H. Morrato, DrPH, MPH; Dennis R. Ownby, MD (Chairperson); James M. Tracy, DO; Yanling Yu, MS, PhD (Consumer Representative)

PADAC Members Not Present (Voting): Nizar N. Jarjour, MD; Richard Weber, MD

DSaRM Members Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Tobias Gerhard, PhD, RPh; Jeanmarie Perrone, MD, FACMT

DSaRM Members Not Present (Voting): Niteesh K. Choudhry, MD, PhD; Karen M. Hopkins, M.D. (Consumer Representative); Marjorie Shaw Phillips, MS, R.Ph., FASHP; Christopher H. Schmid, PhD; Andy S. Stergachis, PhD, RPh; Til Stürmer, MD, MPH, PhD; Linda Tyler, PharmD, FASHP; Almut Winterstein, RPh, PhD, FISPE

Temporary Members (Voting): George Caleb Alexander, MD, MS; Raeford E. Brown, Jr. MD, FAAP; Mary Cataletto, MD; Robert Dracker, MD; Maureen Finnegan, MD; Randall P. Flick, MD, MPH; Lorraine J. Gudas; Sonia Hernandez-Diaz, MD, DrPH; Mark Hudak, MD; J. Steven Leeder, PharmD, PhD; Melanie Dawn Nelson, PhD (Patient Representative); Ruth M Parker, MD; Maria Pruchnicki, PharmD, BCPS, BCACP, CLS; Christianne L. Roumie, MD MPH; Maria E. Suarez-Almazor, MD, PhD; Gary A. Walco, PhD, ABPP; Michael Geary White, MD, PhD, FACC, FAAP

Acting Industry Representative to the Committee (Non-voting): Stuart Green, MD

FDA Participants (Non-Voting): Steven Adah, PhD; CDR David Moeny, RPh, MPH; Judith A. Racoosin, MD, MPH; Sally Seymour, MD

Designated Federal Officer (Non-Voting): Cindy Hong, PharmD

Open Public Hearing Speakers: Marcia Howard, PhD (Consumer Healthcare Products Association (CHPA)); Tracey Rupp, PharmD, MPH (National Center for Health Research); Constance Houck, MD, FAAP (American Academy of Pediatrics)

The agenda proceeded as follows:

Call to Order and Introduction of Committee

Dennis Ownby, MD
Chairperson, PADAC

Conflict of Interest Statement

Cindy Hong, PharmD
Designated Federal Officer, PADAC

FDA Opening Remarks

Sally Seymour, MD

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Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)
Office of Drug Evaluation II (ODE II)
Office of New Drugs (OND), CDER, FDA

FDA PRESENTATIONS

Clinical Pharmacology and
Pharmacogenomics of Codeine

Sheetal Agarwal, PhD, RAC
Clinical Pharmacologist
Office of Clinical Pharmacology
Office of Translational Sciences
CDER, FDA

Codeine for Analgesia; Regulatory History of
Codeine Safety in Children through 2012

Timothy Jiang, MD, PhD
Medical Officer
Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)
ODE II, OND, CDER, FDA

Nonprescription Codeine as an Antitussive in
the Over-The-Counter (OTC) Monograph

Benjamin Bishop, PharmD, MS Reg. Sci.
Division of Nonprescription Drug Products (DNDP) ODE
IV, OND, CDER, FDA

Clinical Considerations for the Use of
Codeine as an Antitussive

Peter Starke, MD
Medical Officer, Associate Director for Labeling
DPARP, ODE II, OND, CDER, FDA

Clarifying Questions to the Presenters

BREAK

FDA PRESENTATION (CONT.)

Drug Utilization Patterns of Codeine-
Containing Products 2010-2014

Rajdeep Gill, PharmD
Drug Utilization Data Analysis Team Leader
Division of Epidemiology II (DEPI-II)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE) CDER,
FDA

Postmarketing Safety Data on Codeine-
Containing Products

Annie Nguyen, RPh
Safety Evaluator
Division of Pharmacovigilance-I
OPE, OSE, CDER, FDA

Epidemiologic Data on Pediatric Emergency
Department Visits Associated with Codeine-
Containing Products
Summary Points

Catherine Dormitzer, PhD, MPH
Epidemiologist
DEPI-II, OPE, OSE, CDER, FDA
Margie R. Goulding, PhD
Epidemiology Team Leader

DEPI-II, OPE, OSE, CDER, FDA

Clarifying Questions to the Presenters

Open Public Hearing

LUNCH

Charge to the Committee **Sally Seymour, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the available data on the safety of codeine use for cough in pediatric patients. Please address the following age groups in your discussion:
 - a) children 0 to younger than 6 years of age
 - b) children 6 to younger than 12 years of age
 - c) children 12 to younger than 18 years of age

***Committee Discussion:** Panel members noted the variability in metabolism of codeine and the potential heterogeneity of treatment effect. Members questioned the efficacy of codeine for cough, but also noted the risk of serious events appeared to be rare. Some members of the committee commented that codeine is not needed as an option for the treatment of cough and poses no benefit compared to the alternative non-narcotic cough suppressants when considering the risks including addiction potential and respiratory depression. The panel recognized that side effects can occur in all ages, but as reflected in the safety data and reported deaths, those under 12 years of age are particularly at risk. Many panel members noted that safety should be looked at in context of efficacy to be able to fully evaluate the risk/benefit profile for codeine products. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss the available data on the safety of codeine use for pain in pediatric patients. Please address the following age groups in your discussion:
 - a) children 0 to younger than 6 years of age
 - b) children 6 to younger than 12 years of age
 - c) children 12 to younger than 18 years of age

Committee Discussion: *Most of the committee members agreed that there are alternative pain treatment options which are metabolized in a more predictable way than codeine and thus don't carry the risks that codeine has related to polymorphic metabolism (i.e., lack of efficacy in poor metabolizers, and risk of respiratory depression in ultra-rapid metabolizers). One member commented on the difficulty of obtaining a prescription for drugs such as morphine vs. codeine due to provider fear of misuse by the adolescent patients or parents of pediatric patients. Some members also commented on the lack of data to effectively make a distinction in risk for the different age groups. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Based upon the discussion of the available safety data with codeine, should the current contraindication for codeine (for pain management in the post tonsillectomy and adenoidectomy setting) be expanded to a contraindication for codeine use for any pain management in children?

As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

- A. Yes – contraindicate for any pain management in children younger than 6 years of age
- B. Yes – contraindicate for any pain management in children younger than 12 years of age
- C. Yes – contraindicate for any pain management in children younger than 18 years of age
- D. No – no change to current contraindication

Provide the rationale for your recommendation and any other labeling recommendations you may have.

A=2

B=6

C=20

D=1

Committee Discussion: *Majority of the panel members agreed that codeine should be contraindicated for any pain management in children younger than 18 years of age. A panel member voting "A" commented that although codeine is harmful in some children, it is effective in providing pain relief for others. Members voting "B" commented that there is insufficient adverse event data available for the older age group, and most deaths occurred in children under 12 years of age. Members voting "C" commented that codeine should not be used unless there is a clear benefit over risk. One member who voted "D" suggested labeling language with codeine recommendations rather than contraindications, as well as warning for obesity, respiratory issues, and sedative use. Please note one member who had originally voted "A" subsequently noted during the explanation of the vote that he wanted to vote "C." The vote count above records the vote as "A." Please see the transcript for details of the committee discussion.*

4. **VOTE:** Based upon the discussion of the available safety data with codeine, should codeine be contraindicated for the treatment of cough in children?

As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

- A. Yes – contraindicate for cough in children younger than 6 years of age
- B. Yes – contraindicate for cough in children younger than 12 years of age
- C. Yes – contraindicate for cough in children younger than 18 years of age
- D. No – no change to current contraindication

A=1

B=5

C=20

D=3

***Committee Discussion:** Majority of the panel members agreed that codeine should be contraindicated for cough in children younger than 18 years of age. The panel member voting “A” commented on the lack of data that is currently available. Members voting “B” commented that the decision to use codeine for cough could be left to clinical judgment. Members voting “C” commented that cough is limited in most cases, and the potential for harm seems greater than the illness. Members voting “D” commented that there is lack of evidence for how cough is suppressed and effectiveness of the alternatives. One member who had originally voted “D” subsequently noted during the explanation of the vote that she wanted to vote “C.” The vote count above records her vote as “D.” Please see the transcript for details of the committee discussion.*

5. **VOTE:** Based upon the discussion of the available safety data with codeine, should codeine be removed from the FDA monograph for over the counter (21CFR341.1; 21CFR341.90) use for the treatment of cough in children?

- A. Yes – remove codeine from the monograph for children younger than 6 years of age
- B. Yes – remove codeine from the monograph for children younger than 12 years of age
- C. Yes – remove codeine from the monograph for children younger than 18 years of age
- D. No – no change to the current monograph for codeine

Provide the rationale for your recommendation and any other recommendations you may have.

A=0

B=1

C=27

D=0

ABSTAIN=1

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Committee Discussion: *Majority of the panel members agreed that codeine should be removed from the monograph for children younger than 18 years of age. In addition, 21 committee members commented that codeine should not be available at all as an over the counter (OTC) medication for any age range and suggested removing it completely from the monograph due to risks of respiratory depression, addiction, opioid abuse, misuse, potential for diversion, variable efficacy, and concerns that consumers may not recognize risk factors for adverse outcomes. The member who voted “B” commented that the number of adverse events reported over the time period that codeine has been in use is insufficient for removal from the monograph. One member abstained from voting, commenting that this question is not within her expertise. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:00 p.m.