Tussionex®
Benefit Risk Balance for Children with Cough

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Inspired by patients.
Driven by science.

Key Messages

UCB reviews all its products on a regular basis including routine pharmacovigilance and evaluation by our internal benefit risk board

Review of Tussionex® included

- modern pharmacovigilance methods
- evolution in clinical practice
- reviewing of literature considering up to date standards

Upon annual review UCB determined that benefit risk balance for use of Tussionex® for cough in children is no longer favorable

Tussionex® (Hydrocodone/Chlorpheniramine Polistirex) History

- 1943: Hycodan® was first hydrocodone product.[1]
- 1976: Advisory Committee determined that hydrocodone was not appropriate for OTC use but was, in effect, “safe and effective” for prescription use.[2]
- 1982: Hycodan® re-evaluated through DESI and found to be “effective for the symptomatic relief of cough”, but was also determined to be a New Drug, thus requiring Sponsor to file an NDA for approval.[3]
- 1983: Tussionex® filed as NDA under article 505(b)(2), and referenced Hycodan® and the monographs for hydrocodone and chlorpheniramine as having been deemed “safe and effective”.[4]
- 1987: Approved; marketed in U.S.[5]
  - 2010: UCB’s authorized generic entered market.[6]

1 NDA 5-213, approved 23 Mar 1943; 2 Federal Register 41 FR 38312, published 09 Sep 1976; 3 Federal Register 47 FR 23809, published 01 Jun 1982;
4 NDA 19-111, submitted 01 Sep 1983; 5 NDA 19-111, approved 31 Dec 1987; 6 ANDA 91632, approved 10 Jan 2010.
DESI = Drug Efficacy Study Implementation; OTC = Over The Counter; NDA = New Drug Application.

Current Tussionex Pennkinetic® Overview

Indication

- Relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and up.[1]

Contraindication

- In children < 6 years of age due to the risk of fatal respiratory depression.[2]

Presentation

- Following FDA recommendation, UCB formulated unit of use presentation (115mL bottle) and discontinued 473mL bottle.[3]

1 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019111s019lbl.pdf; 2 NDA 19-111 Supplement S-015, submitted 30 May 2007, approved 11 March 2008; 3 NDA 19-111 Supplement S-016, submitted 30 Sep 2010, approved 02 Jun 2011. FDA = U.S. Food & Drug Administration.

Tussionex® Safety Summary

Review of UCB safety database: 391 individual drug safety case reports since approval[1]

- 9% (35) of reports are in children <18 years of age

Cumulative exposure of approximately 673000 patient years based on UCB sales data[2]

1 UCB internal data: Argus Database data ran from 01 Jan 1900 to 07 Aug 2017; 2 UCB internal data: available from 01Jan 2007 to 01 Jul 2017.

2016 Tussionex® Benefit-Risk Review

UCB reviewed totality of evidence relating to opioid use for cold/cough in pediatrics including but not limited to:

- 2012 Review of therapeutic options for children with acute cough[1]
- 2015 FDA joint panel of the PADAC and DSRMAC concerning removal of OTC codeine based cough preparations in pediatrics (<18y)[2]
- 2015 EMA review of codeine for cough in children[3]
- 2016 AAP Clinical Report[4]

Hydrocodone metabolized in CYP2D6-dependent manner to more potent hydromorphone:[5]

- Raises possibility of opioid-related adverse effects in ultra-rapid metabolizers[6]
- Hydrocodone metabolism includes several CYPs; rapid metabolism of CYP2D6 appears to have only minor impact[7]

1 Paul (2012) Lung, 190: 41; 2 https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm475975.pdf; 3 European Medicines Agency (24 April 2015) EMA/249413/2015; 4 Tobias et al (2016) Pediatrics 138: e20162396; 5 Cone et al (2013) J Analyt Toxicol 37: 486; 6 Madadi et al (2010) Pediatrics 126: e986; 7 Cone et al (1978) Drug Metab Disposit 6: 488. CYP = Cytochrome P; DSRMAC = Drug Safety Risk Management Advisory Committee; FDA = U.S. Food & Drug Administration; OTC = Over The Counter; PADAC = Pulmonary-Allergy Drugs Advisory Committee.

Ongoing FDA Prior Approval Supplement Submission

As a result of our recent evaluation UCB filed label supplement to limit to patients 18 years and older[1]

- Already contraindicated under 6 years of age[2]

1 NDA 19-111 Supplement S-020, submitted 12 Jan 2017, under review; 2 NDA 19-111 Supplement S-015, submitted 30 May 2007, approved 11 March 2008.
FDA = U.S. Food & Drug Administration.

2016 Tussionex® Benefit-Risk Summary

Best treatment for cough is management of underlying disorder[1]

Review of safety and efficacy data for patients 6-18 years

- On cumulative review of UCB and literature safety data no new safety concerns were identified[2]
- On cumulative review of available data, regulatory reports and practice guidelines, no robust evidence for relief of cough/upper respiratory symptoms associated with allergy/cold could be identified in patients 6-18 years[2]

Conclusions/Proposed actions

- Using modern pharmacovigilance methods UCB determined benefit-risk for Tussionex® in children was no longer positive[2]
- Therefore, UCB submitted a prior approval supplement to restrict indication/usage of Tussionex® to patients ≥ 18 years of age[3]

1 Irwin et al (2006) Chest 129: 1S; 2 UCB internal data: Results of Tussionex® Benefit-Risk Assessment 2016; 3 NDA 19-11 Supplement S-020, submitted 12 Jan 2017, under review.