CHPA

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Consumer Healthcare Products Association

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1. EXECUTIVE SUMMARY

1.1 Introduction

In the August 16, 2007, *Federal Register*, FDA announced a joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee to discuss the safety and efficacy of over-the-counter (OTC) cough and cold medicines marketed for pediatric use. A citizen petition was submitted to the FDA in March 2007 which raised concerns about the safety and efficacy of OTC cough and cold medicines used in children under 6 years of age.

The Consumer Healthcare Products Association (CHPA) is the national trade association representing the leading manufacturers and distributors of OTC medicines and dietary supplements in the United States, including cough and cold medicines. As such, we have an interest and expertise in the subject matter of the Advisory Committee meeting and are providing background information for the committee to review prior to the meeting.

The documents provided in this briefing book address important issues to consider in relation to the safety and efficacy of OTC pediatric cough and cold medicines, including antitussives, expectorants, nasal decongestants, antihistamines, and combination products. CHPA has conducted a review of the available data related to the safety and efficacy of the ingredients available in this category, including market research with caregivers and healthcare professionals who use them. As outlined, the materials included address the following areas:

- The importance and benefits of treatment of cough and cold symptoms
- Efficacy of OTC cough and cold medicines in adults and children
- Overview of pharmacokinetics of cough and cold ingredients
- Safety analyses of published and other public data
- Caregiver and healthcare professional insights
- Recommended action plan
- Our priority is to ensure that parents and families have access to the best possible OTC medicines available today and that caregivers have the resources and information available to use these medications safely and appropriately.

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1.2 Background

OTC cough and cold medicines have been available to consumers and used by parents and physicians for decades. They continue to play an important role in reducing symptoms of the common cold, and it is accepted medical practice to recommend these medicines for symptomatic relief. These medicines do not cure the conditions themselves, but rather provide symptomatic relief for children and adults, as well as lessen the economic burdens caused by colds.

The ingredients under discussion have been available to consumers through the OTC monograph process. Safety, effectiveness, and labeling reviews by experts were conducted on each of these ingredients, resulting in the FDA's assessment of these ingredients as generally recognized as safe and effective. Through the OTC Review, industry and consumers have relied on this regulatory framework for the availability of safe and effective medicines. Over the past few months, however, CHPA and its member companies have conducted our own review of both the safety and efficacy of OTC cough and cold medicines in children ages 0 to under 12 years of age.

1.3 Efficacy

While there are significant data to show the efficacy of these products in adults, several smaller placebo-controlled studies in children did not show significant differences in favor of cough and cold medicines. These results were likely because of the difficulty in evaluating the symptoms of a cold in this young age group. While years of practical application by both doctors and parents using these medicines demonstrates that these ingredients are effective in relieving symptoms of cough and cold in children, it is important to affirm the science supporting these ingredients by conducting additional research under current scientific standards.

Since the OTC monographs were developed for these ingredients, science has evolved that can be brought to bear on the questions before the advisory committee. Investigators now have the practical experience with pediatric research to conduct more comprehensive pharmacokinetic (PK) studies in children between the ages of 2 and 12 years of age. Companies are already

starting to gather important PK data in children, and CHPA and its members are committed to initiating relevant PK studies in key ingredients included in the monograph for OTC cough and cold medicines. Available PK studies in some ingredients confirm the dosing recommendations under the OTC monograph. These further studies should confirm or refine the dosing amounts currently under the OTC monograph.

1.4 Safety

In addition to our efficacy review, CHPA along with outside experts has conducted a review of safety data for OTC cough and cold medicines. This review confirmed that recommended doses of OTC cough and cold medicines are well tolerated in children. Across all age groups, our only safety findings were the known side effects of OTC ingredients, such as drowsiness. The review did reveal rare adverse events, including fatalities that have been reported in association with overdose and misuse of OTC cough and cold medicines. Given the extensive use of these medicines serious adverse events in children of all ages are extremely rare.

Analyses were done for age groups 0 to under 2, 2 to under 6 and 6 to under 12 years of age. Fatal outcomes were most often reported in children less than 2 years of age, either resulting from caregivers administering more than the recommended dose (overdose) or secondary to accidental overdoses following ingestion of these medicines by curious young children who gain accidental and unsupervised access. Data from the American Association of Poison Control Centers shows that in children less than 6 years of age, accidental exposures of OTC cough and cold medicines due to inadequate poison prevention measures result in the highest incidence of overdose, consistent with medications in general. Overdoses from OTC cough and cold medicines resulting in toxicity and requiring healthcare evaluation and treatment are rare.

Data from various sources document that medication errors with OTC cough and cold medicines in children, especially children less than 2 years of age, may lead to overdose. Several high-risk scenarios and behaviors with the administration of these medications to children were identified. These include administering much higher than recommended doses, accidental ingestion,

concomitant use of other medications including prescription drugs, and the misuse of monograph antihistamines for sedation of children.

This review supports the safety of OTC cough and cold medicines when used according to the label as outlined in the OTC monograph. Safety data from prospective clinical trials provides support for performing pharmacokinetic studies in children from 2 to less than 12 years of age.

1.5 Parents and Healthcare Providers

Through research, we know in general that parents understand how to use these medications and feel very comfortable administering them to their children. Most parents consult a healthcare professional before using OTC cough and cold medications, especially in very young children. We also know that pediatricians have the most impact on parents' decisions to give their children OTC cough and cold medicines. While pediatricians, along with other healthcare providers, do recommend using these medications in children 2 years of age and above, they are less likely to recommend OTC cough and cold medications for children less than 2 years of age. Additionally, research shows a lack of understanding among caregivers about the active ingredients.

1.6 Recommendations

Based on the data, findings, and analyses presented in this book, CHPA and its member companies are taking the following steps to encourage the appropriate use of all of these medicines:

- We recommend that the label be changed in all OTC cough and cold medicines to read "Do Not Use" in children 0 to under 2 years of age.
- We recommend that additional language be added to the label of antihistamines currently under the OTC monograph to indicate "Do not use to sedate children."
- We are committed to supporting a national education campaign targeted at caregivers and healthcare professionals to raise awareness of these label changes and reinforce the safe use of these medicines in all appropriate age groups.
- We are committed to conducting a prospective safety study.

- We are committed to conducting pharmacokinetic studies of all relevant ingredients in children 2 to under 12 years of age where additional data is needed.
- We are committed to working in close cooperation with FDA and other experts to identify strategies to bridge efficacy data, including the development of validated, pediatric pharmacodynamic or clinical symptom endpoints.

CHPA and its member companies have a long history of educating consumers on the safe use of OTC medicines and have taken the lead on many important initiatives over the years. From child resistant packaging to tamper-evident packaging and the development of the OTC Drug Facts label in conjunction with FDA, CHPA has been proactive and unwavering in its commitment to providing the highest quality medicines to the millions of American families who rely on them each and every day, as well as the information and tools to use these medicines appropriately. We see the recommendations and initiatives outlined in this document as a continuation of this long standing commitment.

The materials provided in this document reflect the collective work and views of the following CHPA member companies who currently market OTC cough and cold medicines for children:

- Adams Respiratory Therapeutics
- McNeil Consumer Healthcare
- Novartis Consumer Health, Inc.
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Since the OTC monographs were developed for these ingredients, science has evolved that can be brought to bear on the questions before the advisory committee. Investigators now have the practical experience with pediatric research to conduct more comprehensive pharmacokinetic (PK) studies in children between the ages of 2 and 12 years of age. Companies are already

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2 THE IMPORTANCE OF TREATMENT OF COMMON COLD SYMPTOMS

2.1 Key Points

- Symptomatic treatment of the common cold is well accepted medical practice in adults and children
- There are significant economic burdens due to colds
- While there is limited efficacy data from clinical trials, survey data suggest that both healthcare professionals and parents believe that OTC cough and cold medicines are beneficial in the symptomatic management of colds.

2.2 Symptomatic Relief

The common cold is recognized as the most common infectious syndrome of humans [Eccles 2005, Gwaltney 2002] with adults experiencing 2 to 4 symptomatic infections each year and children experiencing 6 to 8 [Heikkinen and Jarvinen 2003]. Symptomatic treatment of the common cold in adults and children has long been established as acceptable medical practice because there is no effective preventive measure or treatment available for the underlying viral etiology [Turner 2001]. Consequently, medical intervention is limited to the symptom relief and reduction of associated morbidity, facilitating the return to normal function while the condition resolves naturally. For the vast majority of uncomplicated cold episodes in adults and children, management of symptoms with OTC cough and cold medicines (antitussives, nasal decongestants, antihistamines, and expectorants) helps to achieve this objective.

2.3 Prevalence and Pattern of Cold Symptoms in Children and Adults

In the United States, cough is the most frequent complaint for which patients seek medical attention, and nasal congestion is mentioned in the top 20 reasons for a doctor's office visit [Woodall 2004]. Both cough and nasal congestion are symptoms frequently associated with the common cold.

Children of all ages, as well as adults, experience nasal symptoms (e.g. congestion and rhinorrhea) and cough as a result of the common cold. However, the prevalence and pattern of symptoms vary with age. In a longitudinal prospective study that enrolled infants from birth until one year of age with acute respiratory infections, 96% of the 984 infants had a runny/obstructed nose (rhinorrhea and nasal congestion) and 76.8% had a cough [Kusel

2006]. Table 2.1 summarizes the symptoms reported by parents or guardians in this study. Similar to adults, the infants experienced nasal symptoms and cough. However, unlike adults, at least one third of the infants also experienced a rattly or wheezy chest.

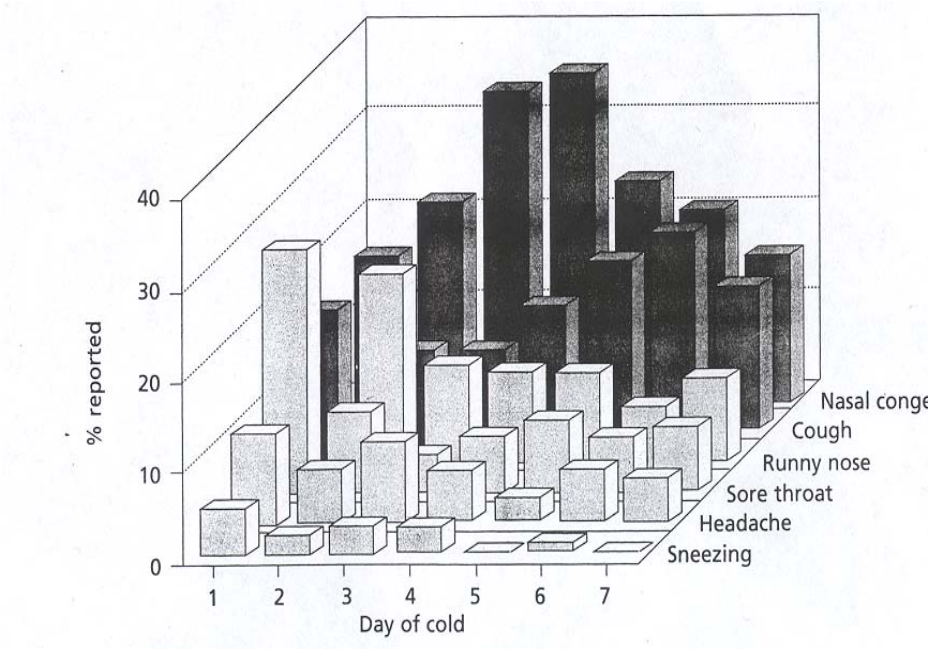
Table 2.1 Symptoms From 984 Episodes of Acute Respiratory Infections in Infants from Birth to 12 Months of Age

Symptom	Number (%)
Runny/obstructed nose	945 (96.0)
Cough	756 (76.8)
Rattly or wheezy chest	329 (33.4)
Fever	238 (24.2)
Wheeze present	95 (9.7)

A recent study examined cold symptoms in 81 predominantly school-aged children, ranging from 2 through 12 years. Symptom diaries on the children were kept for 10 days following onset of a cold. The most common reported symptoms at their maximum prevalence over 10 days were nasal congestion (88%), runny nose (72%), cough (69%), and sneezing (55%) [Pappas in press]. Fever and headache were each reported in 15% of children at onset of the cold.

Research in naturally acquired and artificially induced colds confirms that the symptoms tend to occur in a predictable pattern over the 7 to 10 days of a typical uncomplicated infection (Figure 2.1) [Gwaltney 2002, Tyrrell 1993, Gwaltney 1967, Witek 1992].

Figure 2.1 The clinical course of acute upper respiratory tract infection [adapted from Witek 1992]



In addition, epidemiological research in over 1,000 common cold patients by the Bristol Myers Company confirmed that over the period of a normal, uncomplicated infection, 32-52% of patients had as many as 4 of the key signs and symptoms of the common cold simultaneously (Table 2.2) [Bristol Myers Company Petition to US FDA 1979].

Table 2.2 Multiple symptoms occurring simultaneously during the common cold [Bristol Myers Company Petition to US FDA 1979]

Day of Illness	% of patients with 4 symptoms
1	32.31
2	44.25
3	51.06
4	47.76
5	49.06
6	52.63
7	38.89
8 or more	49.18

These data, and those of Gwaltney in naturally acquired colds, coupled with the results of Tyrrell and Turner from induced colds, emphasize the medical desirability for treatment of multiple symptoms [Gwaltney 1967, Tyrrell 1993, Turner 1996]. Additionally, the effects of these symptoms are often most bothersome to patients in the evening, particularly as they retire to bed, and can affect rest, and subsequent performance the following day [Drake 2000]. Similarly, in school-aged children, it has been shown that multiple coincident symptoms are part of the cold, in particular nasal symptoms and cough [Pappas in press]. Based on the range of symptoms experienced by patients and the coincidence of multiple symptoms, it is reasonable to have OTC combination cough and cold medicines that can relieve symptoms of cough, nasal congestion, and rhinorrhea.

2.4 Economic Burden of Colds

Morbidity associated with the common cold is known to have a considerable social cost. In the United States, the magnitude of the economic impact has been estimated at $25 billion lost due to non-influenza common cold, of which $16.6 billion is lost on-the-job productivity, $8 billion due to direct employee absenteeism, and $230 million due to caregiver

absenteeism [Bramley 2003, Fendrick 2003]. It seems reasonable to suggest that much of this cost is due to care for children, as the common cold is the most prevalent childhood illness, and it occurs with greater frequency in children compared to adults. Adults typically experience 2 to 4 symptomatic infections each year and children experience 6 to 8 [Heikkinen and Jarvinen 2003].

Among children, there is absenteeism from school due to the common cold estimated at 189 million school days annually and increased healthcare provider interaction [Fendrick 2003]. Lack or reduction of availability of symptomatic cough and cold preparations would considerably impact the healthcare system in the form of additional physician visits in a search of symptom resolution, and potentially an increase in unnecessary and inappropriate antibiotic prescribing since many children with colds are given prescriptions for antibiotics [Nyquist 1998]. Inappropriate use of antibiotics would provide minimal therapeutic benefit, add substantially to healthcare costs, and raise antibiotic resistance concerns [Steinman 2003].

Economic data on the impact of OTC cough and cold medicines is limited but suggests that these products lessen the economic burden associated with colds. Temin suggested that the availability of OTC cough and cold medicines contributed to an average reduction in physician visits in the U.S. by 110,000 per year over a 14 year period from 1976 to 1989 [Temin 1992]. In terms of medical costs of physician visits and costs of prescription drugs, another study estimated that OTC cough and cold medicines save consumers $3 billion per year [Kline 1997].

2.5 Exposure Estimates

Using information and estimates from household panel data provided by Information Resources, Inc., we estimate that there were approximately 288 million units of pediatric cough and cold products sold in the last 3 years ending December 31, 2006. This translates into approximately 95 million units sold annually. An estimated 39% of households purchase these products in this period, meaning there were a projected 44 million buyers.

2.6 Benefits to Children and Parents

There are data from controlled clinical trials evaluating efficacy of OTC cough and cold medicines in the pediatric population (see Section 3, Efficacy). It should be noted that the small sample size and inconsistent endpoints in these trials can make them difficult to

interpret. However, the benefits of OTC cough and cold medicines to the pediatric population have been demonstrated in survey studies of both healthcare providers and caregivers.

In 2007, CHPA commissioned a national survey of 3000 Americans on their use of OTC products to treat cough symptoms resulting from the flu, cold, or other respiratory ailments [CHPA 2007a]. In 648 households that had children age 18 and under, 73% of parents and caregivers indicated that they administered an over-the-counter cough medicine to the child in their home who was experiencing a cough, regardless of the age of the child. A total of 91% of parents and caregivers reported that use of OTC cough remedies helped them or the child feel more comfortable. Importantly, 89% of adults, parents, and caregivers indicated that the cough remedies they used effectively helped them or the child in their household cough less. More than three-quarters of adults, parents and caregivers also indicated that cough remedies helped them and the child both function and sleep better.

Another recent survey was conducted among 1,000 adults living in the United States, and a stand-alone survey of 150 adults with children ages 12 and under in the home, to assess common practices among adults who have children experiencing nasal congestion [CHPA 2007b]. When adult Americans were asked about common practices used when a child living in their home experiences nasal congestion, the most commonly reported action was giving the child an OTC medication. In total, 70% of respondents reported using an OTC medication to treat nasal congestion. This practice appears to be the most common practice across all age groups, genders, and regions of the country.

The second most commonly reported practice in treating a child with nasal congestion is talking to a doctor (32%). This practice is most prevalent in the South, where 50% report talking to a doctor when their child is experiencing nasal congestion.

Table 2.3 indicates the level of agreement with each of the 4 statements included in the CHPA study. Please note that the percentages add to more than 100%, as this question allowed more than one response.

Table 2.3 Survey Results - What Most Americans Do to Treat a Child with Nasal Congestion

	Total Agree
Use an OTC medicine, that is, a medicine that you can buy without a prescription	70%
Talk to a doctor	32%
Use a prescription medicine	24%
Wait or do nothing	18%

Only 3% of respondents who administered an OTC medication to treat nasal congestion reported that the medication had no positive effect on the child. The remaining 97% report at least one positive benefit (Table 2.4). These include helping the child feel more comfortable, breathe easier, function better and relieve a runny nose. As seen in the table (Table 2.4), 8 in 10 (81%) reported that an OTC medication helped their child feel more comfortable. These benefits are widely reported across all segments of the population.

Table 2.4 Survey Results – What Caregivers Believe are the Benefits of OTC Decongestants

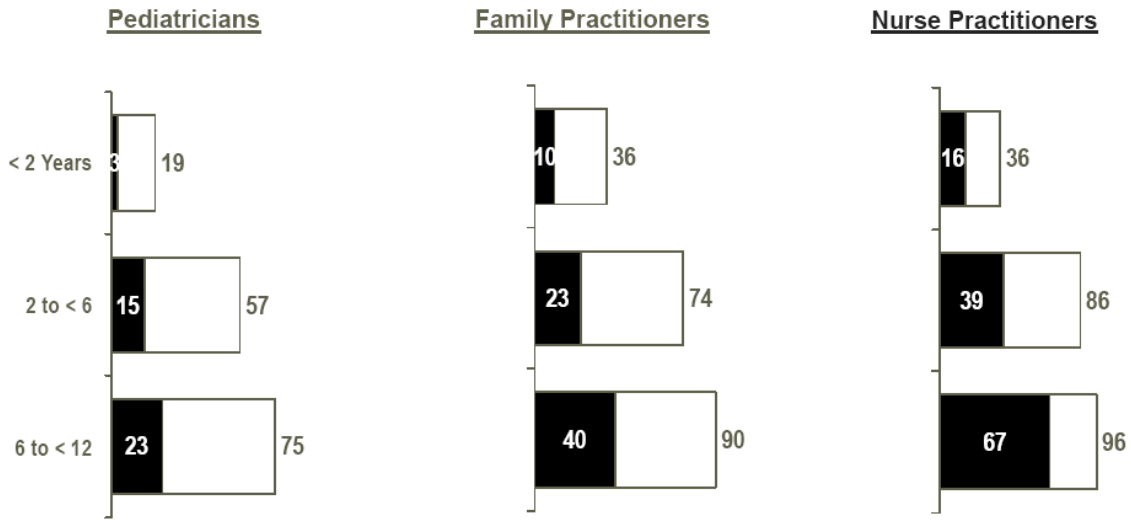
	Total Agree
It helped them feel more comfortable	81%
It helped them breathe more easily	72%
It made their nose less runny	69%
It helped them function better	60%
None of the above/No effects	3%

These findings show that the majority of adult Americans turn to OTC medications as a first response when a child in the home is experiencing nasal congestion. There is also common belief that these medications offer multiple benefits for the child.

Likewise, a recent survey of 310 healthcare professionals including pediatricians, family practitioners, and nurse practitioners was conducted by Wyeth to obtain their opinions on the use of OTC cough and cold medicines, specifically, antihistamines, decongestants, antitussives, and expectorants, in three pediatric age groups: under 2 years, 2 to under 6 years and 6 to under 12 years [Wyeth 2007]. In general, the results of the survey indicated that:

- The majority of healthcare practitioners including pediatricians are in favor of recommending OTC cough and cold medicines for their pediatric patients in the 2 to under 6 and 6 to under 12 year age groups (see Figure 2.2).
- The top 4 symptoms that triggered medical professionals to recommend the use of an OTC cough and cold product were: fever, cough, stuffy nose, and difficulty sleeping.

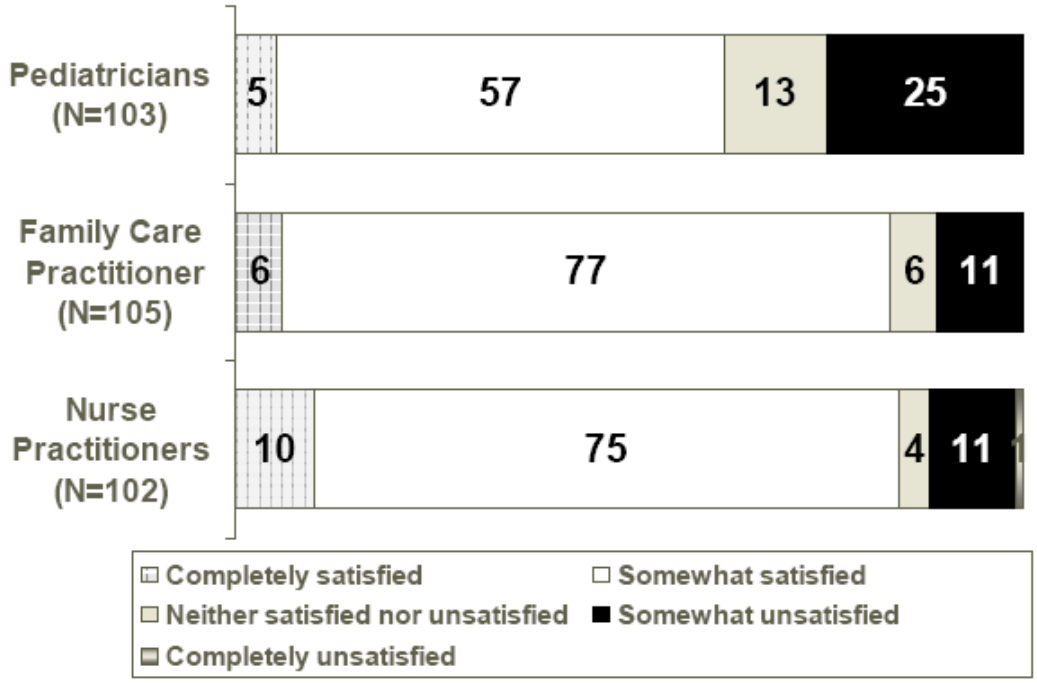
Figure 2.2 Healthcare Professional Opinions on the use of OTC Products to Treat Cough and Colds by Age Group



Numbers in the blackened areas reflect the percent of healthcare professionals (by discipline) that were very favorable towards OTC cough and cold medicines. The open area reflects the proportion of healthcare professionals that were somewhat favorable. The total percent of healthcare professionals that were very favorable or somewhat favorable is indicated at the end of each bar.

The survey also found that the age of the child and symptom severity are 2 key drivers that influence the recommendations of OTC cough and cold medicines by medical professionals. The majority of medical professionals cited a specific dose when OTC cough and cold medicines were recommended. Overall, the majority of healthcare professionals perceived that parents are at least somewhat satisfied with the effectiveness of their recommended OTC cough and cold medicines (Figure 2.3). Furthermore, medical professionals believe that the major benefits of OTC cough and cold medicines are symptom relief and allowing the child to get a good night of sleep.

Figure 2.3 Healthcare Professionals Perception about Parent Satisfaction with Recommended OTC Cough and Cold Medications for their Children (%)



When questioned about what they would recommend if pediatric OTC cough and cold medicines were no longer available, most medical professionals would recommend a home therapy (e.g. humidifier, normal saline nose drops). They also indicated that prescription drugs would be more common and that proper dosages of adult medications would be an option for older children.

In summary, these data suggest that healthcare practitioners and parents believe that OTC cough and cold medicines do provide benefit to the pediatric population. In contrast to the view of a recently submitted Citizen Petition [Sharfstein 2007], the results from this healthcare practitioner survey suggest that there is no consensus among physicians that OTC cough and cold medicines should be restricted for use in the 2 to under 6 year age group, and that, in fact, only a minority of them favored the use of the products for the 0 to under 2 year old group. Given the 95 million units of pediatric OTC cough and cold medicines sold annually and the long history of safe use with these products at recommended doses, it is more than reasonable to conclude that consumers derive some benefit from them.

3 EFFICACY OF OTC COUGH AND COLD MEDICINES

3.1 Key Points

- Evidence for the efficacy and safety of OTC cough and cold medicines based on randomized, placebo-controlled trials in adults are prevalent in the literature.
- The results of pediatric studies of OTC cough and cold medicines have been inconclusive to date.
    - There are considerable challenges and limitations to the study of cough and cold medicines in pediatrics related to study design and lack of sensitive relevant endpoints.
    - The majority of pediatric randomized, controlled trials (RCTs) have been underpowered.
    - Recommendations by professional, authoritative bodies to not use certain ingredients in young children relate, for the most part, to the lack of robust clinical trial data in this patient population.
- CHPA concludes that it would be beneficial to expand the body of evidence for the use of cough and cold medicines in children.
    - Studies must be appropriately powered to achieve statistical significance.
    - Appropriate efficacy endpoints based on the mechanism of action (MOA) of the test medications must be employed.
    - The field will be advanced by the development of robust, validated methodology for evaluating the signs and symptoms of the common cold.

3.2 Introduction

In the Citizen Petition, Docket # 2007P-0074, Sharfstein *et al* contend that OTC pediatric cough and cold medications are *not* generally recognized as safe and effective (GRASE). CHPA disagrees with this assessment, and this section reviews the efficacy results upon which this opinion is based.

There are a number of drug classes employed in the symptomatic treatment of the common cold. Each class of drugs exerts a particular mechanism of action or symptom-specific effect, and for some classes there is more than one compound available. Several OTC cough and cold products were approved under a New Drug Application (NDA), and the remainder of ingredients are addressed in the “Cold, Cough, Allergy, Bronchodilator, and

Antiasthmatic Drug Products for Over-the-Counter Human Use" monograph 21 CFR 341. Products approved under an NDA demonstrated efficacy and safety as determined by rigorous review prior to approval by FDA. Further, monograph ingredients underwent a structured review process to achieve inclusion in the monograph. The basis for the OTC monograph for these ingredients is that they are GRASE (Category I = generally recognized as safe and effective for its intended use). Cough and cold medications are available as monotherapy and in various combination products as permitted by the respective NDA or monograph. Recommended dosing is provided in these documents.

Clinical studies have established safe doses for adults. There are a number of positive efficacy studies for each medication in adults. Yet, evaluating the effectiveness of cough and cold medications is challenging. The lack of sensitive, specific, and validated methodology to evaluate common cold symptoms; the magnitude of the placebo effect; and the subjective nature of many of the symptoms has resulted in inconsistent results across adult trials and confounded the conduct and interpretation of pediatric clinical trials.

At present, there is a lack of robust efficacy data for cough and cold medicines in children. However, pediatric research networks have expanded, and study methodology and pharmacologic knowledge have evolved. Therefore, it may now be possible to effectively readdress the study of these products in children. Such studies would provide additional population pharmacokinetic data which underlay safe and effective dosing with these products. An industry proposal for a clinical trial program is included in this document (Section 7).

For the purposes of our analysis of safety and efficacy of OTC pediatric cough and cold ingredients, we focused on the most prevalent ingredients, as listed below:

Therapeutic Category	Active Ingredients	Sample Indications
Nasal Decongestants	Pseudoephedrine HCl Phenylephrine HCl	Temporarily relieves • nasal and sinus congestion • stuffy nose • clogged up nose .
Antihistamines	Chlorpheniramine Maleate Diphenhydramine HCl Brompheniramine Maleate Doxylamine Succinate	Temporarily (relieves, alleviates, decreases, or reduces) these cold symptoms: • runny nose • sneezing
Antitussives	Dextromethorphan HBr Diphenhydramine HCl	Temporarily helps • you cough less • to suppress the impulse to cough • reduce the cough reflex that causes coughing • decrease the intensity of coughing
Expectorants	Guafenisin	Temporarily helps • loosen phlegm and bronchiole secretions •makes cough more productive

3.3 Efficacy Data

3.3.1 Adult Efficacy Data

There are a number of randomized, double blind, placebo-controlled studies of cough and cold therapies in adults, many of which demonstrated statistically and clinically significant improvements in symptoms, and some of which may have been considered as a basis of support for the OTC monograph. Described in this section are published, randomized, double blind, placebo-controlled studies in adults that evaluated cough and cold medications, which overall suggest that adults do accrue significant benefit from these drugs. Reviews by independent committees (Cochrane Library, The American College of Chest Physicians, The European Respiratory Society, The American Academy of Pediatrics) of each drug class or of this therapeutic area, are presented where they exist. Listings of published placebo-controlled randomized clinical trials (RCTs) by drug, by age (adult and pediatric) along with study designs, sample sizes, and results are found in Appendix 1 of this document.

3.3.1.1 Effect of antihistamines on nasal symptoms associated with the common cold

A meta-analysis of 9 studies by D'Agostino summarized the efficacy of antihistamines (chlorpheniramine (n=202), doxylamine (n=307) and placebo (n=518)) in reducing the severity of runny nose and sneezing, and concluded that, "Antihistamines are statistically significantly more effective than placebo in reducing the severity of runny nose and sneezing associated with the common cold. Most importantly, the differences between antihistamines and placebo were clinically relevant based on the goal of therapy criteria established a priori. The benefits of antihistamine therapy in the common cold appear to be clinically achievable." The goal of therapy, predefined by the authors as a 50% reduction in the mean symptom score, was significantly better for antihistamines (vs placebo) for both sneezing and runny nose, indicating that the observed treatment effects were clinically, as well as statistically, significant. [D'Agostino 1998].

In the literature, RCTs of antihistamine monotherapy in adults with the common cold are positive overall. Of the 6 studies identified, 4 showed efficacy in control of various cold symptoms. The other 2 studies did not demonstrate efficacy:

- Howard studied chlorpheniramine (CHLOR) 4 mg 4 times daily for 6 days in subjects with signs and symptoms of the common cold, using subjects' subjective assessments of symptoms and physician assessments. CHLOR (n=133) was superior to placebo (n=138) in lessening the degree of symptoms, with statistically significant differences in the subjects' overall evaluation favoring CHLOR on the first day (27.1% vs 18.8%) and as late as the seventh day (71.4% vs 63.8%). Other measures trended in favor of CHLOR [Howard 1979].

- Crutcher and Kantner studied adults within 48 hours of onset of cold symptoms. They were given CHLOR 4 mg (n=52) or placebo (n=54) 4 times daily for 7 days. Subjective evaluation of symptoms by subjects and of signs by physicians showed significant relief in cold symptoms and a clear trend toward reduction of signs of a cold [Crutcher 1981].

- Doyle gave CHLOR 4 mg (n=19) or placebo (n=18) every 4 hours for 5 days to subjects with rhinovirus-induced colds. Objective assessments of nasal patency (by rhinometry), eustachian tube function (by 9-step test and sonotubometry), middle ear pressure (by tympanometry), and nasal clearance (by dyed-saccharin technique), and quantification of nasal secretions and evaluations of symptoms by subjects, demonstrated CHLOR to be effective in decreasing sneezing and in increasing mucociliary clearance [Doyle 1988].

- Gaffey studied CHLOR 4 mg (n=10) vs placebo (n=11) 4 times daily for 4 days in subjects who were intranasally inoculated with rhinovirus, measuring expelled nasal mucus weight and used nasal tissue counts, with monitoring of clinical symptoms to determine frequency and severity of clinical illness. CHLOR was not found to have a significant effect on nasal symptoms or mucus production [Gaffey 1987].

- Gwaltney and Druce induced colds and administered brompheniramine (BROM) 12 mg (n=113) or placebo (n=112) twice daily, obtaining weight of nasal secretions and subjective symptom scores. Mean nasal secretion rates for BROM were significantly lower vs placebo on all treatment days. Similar results were seen with subjective symptom scores including rhinorrhea, sneezing counts, and sneezing severity [Gwaltney 1997].

- Eccles studied doxylamine (DOX) 7.5 mg (n=345) vs placebo (n=343) 4 times daily for 9 doses in subjects with colds, evaluating day 2 subjective assessment of runny nose and sneezing, and nasal secretion rates. There were statistically significant differences favoring DOX for sneezing and runny nose on days 2 to 3, and days 1 to 3, respectively. Outcome for nasal secretions were not reported [Eccles 1995].

The Cochrane Review of antihistamines (AH) for the common cold included 32 papers that had 35 comparisons; 22 trials studied AH monotherapy and 13 trials studied combinations of AH with other medications. A total of 8930 patients were involved. The conclusion was that antihistamines alone are not an effective treatment for the common cold, but might have a small effect in combination with decongestants. Combinations of antihistamines with decongestants were not effective in small children based on this review. In older children and adults, most trials show a beneficial effect on general recovery as well as on nasal symptoms.

3.3.1.2 Decongestants

Five placebo-controlled randomized studies of pseudoephedrine (PSE) as monotherapy (one study also included a PSE with ibuprofen arm), and one placebo-controlled study using PSE with aspirin, and PSE with paracetamol (acetaminophen), found PSE effective in reducing symptoms of nasal congestion. No negative placebo-controlled RCT of PSE was identified. Although the efficacy of phenylephrine (PE) 10 mg has recently been questioned, a recent meta-analysis by Kollar demonstrated that PE 10 mg produces a significant improvement in nasal airway resistance.

Bye compared PSE 60 mg alone (n=61) and in combination with triprolidine 2.5 mg (n=55) vs placebo (n=60) in adults with the common cold. Sneezing, nasal obstruction, and overall responses to treatment were significantly improved with PSE and PSE with triprolidine compared with placebo [Bye 1980].

Sperber compared PSE 60 mg alone (n=23) and in combination with ibuprofen 200 mg (n=23) vs placebo (n=10) in young adults intranasally inoculated with rhinovirus 30 hours before initiating treatment. Total symptom scores compared to placebo were reduced by 59% with the combination and by 48% with PSE alone, but only nasal symptom scores were substantially different between the groups; there was significantly less rhinorrhea (nasal secretion weight) vs placebo in both PSE treatment groups (41% for PSE and 30% for the combination vs placebo); nasal patency was most improved with the combination [Sperber 1989].

Taverner compared single-dose PSE 60 mg (n=25) with placebo (n=27) in subjects with the common cold (<5 days of symptoms) and moderate-to-severe nasal congestion. Objective measurement of nasal cross-sectional area and volume by acoustic rhinometry, demonstrated significant increases with PSE in total nasal minimum cross-sectional area (AUC increased 7% over placebo) and nasal volume (AUC increased 11% over placebo) [Taverner 1999].

Eccles studied PSE 60 mg (n=119) and placebo (n=119) 4 times daily in subjects with moderate nasal congestion associated with the common cold (onset <72 hours). Objective measurement of nasal airway resistance by posterior rhinometry and objective scoring (VAS) of nasal congestion every hour for 4 hours after first dose on day 1 and after the last dose on day 3 revealed significantly decreased nasal airway resistance 2 to 4 hours after first dose of PSE on day 1, and 0 to 4

hours after last dose on day 3 (percent reduction in geometric mean relative to placebo, 10.4% to 20.5%); lower subjective congestion scores were statistically significant after one dose of PSE on day 1, but not after multiple doses on day 3 [Eccles 2005].

Latte compared PSE 60 mg to placebo (total n=216) administered 4 times daily for 3 to 4 days using objective measurement of nasal airway resistance by posterior rhinometry and objective scoring of symptom severity using a VAS. They found decreased nasal airway resistance and improved symptoms of congestion with PSE [Latte 2006].

Loose evaluated PSE 60 mg with aspirin 1000 mg (n=161) vs placebo (n=162) in subjects with nasal congestion associated with common cold, as well as comparisons of the combinations, PSE 30 mg with aspirin 500 mg (n=161) vs PSE 60 mg with paracetamol (acetaminophen) 1000 mg (n=159). They employed subjects' subjective assessments of nasal congestion, with primary efficacy variable being the area under the curve (AUC) for differences from baseline on a nasal congestion scale in first 2 hours after treatment. All active treatments were statistically superior to placebo. PSE 60 mg with aspirin was efficacious for all subjects for the entire 6 hours, with significant results for nasal congestion and relief of nasal stuffiness [Loose 2004].

Cohen compared single doses of phenylephrine (PE) 10 mg, 15 mg, and 25 mg, and placebo in 48 subjects with nasal congestion associated with the common cold, using objective determination of nasal air flow/resistance by electronic posterior rhinometry and subjects' subjective estimations of nasal congestion. Results included decreased nasal flow/resistance with all three doses of PE tested, apparent at 15 minutes, maximal between 30 and 90 minutes, and still present 120 minutes after treatment. (Although not described by the authors, the figures indicate that the differences for all three doses were approximately 20% to 50% greater than for placebo, for both nasal flow and nasal symptom scores) [Cohen 1972].

Kollar performed a meta-analysis of the efficacy of a single dose of phenylephrine (PE) 10 mg compared to placebo in adults with acute nasal congestion due to the common cold. Seven cross-over studies (n=113) and a reanalysis of a parallel group study (n=25 in both verum and placebo group) support the effectiveness of a single oral dose of PE 10 mg as a decongestant in adults with acute nasal

congestion associated with the common cold. Nasal airway resistance (NAR) was measured in these studies. The mean reduction from baseline in NAR was approximately ⅔ to 2 times greater for phenylephrine than for placebo between 15 and 90 minutes after dosing [Kollar 2007].

There were no studies in children meeting the criteria for inclusion in the Cochrane Review of nasal decongestants. Seven adult studies were included (one of which studied an intranasal decongestant, n=106; the others were oral decongestant studies n= 630) and it was concluded that nasal decongestants offer a modest improvement in nasal congestion supported by a significant decrease in measured nasal airways resistance. Adverse effects on treatment were no more likely than with placebo, and the most common adverse effect on treatment was insomnia (5%). The authors concluded, “There is insufficient data on the use of these medications in children and therefore they are not recommended for use in children younger than 12 years of age with the common cold.”

3.3.1.3 Antitussives

A review of the literature found 3 randomized placebo-controlled trials of dextromethorphan (DXM) and a meta-analysis of 6 other DXM RCTs in the treatment of cough associated with the common cold. Although one trial was negative, the other trials found DXM efficacious and well-tolerated in the treatment of acute cough associated with colds, reducing cough counts, latency between coughing bouts, and cough effort.

Tukiainen studied DXM 30 mg (n=36) and DXM 30 mg with salbutamol 2 mg (n=38) vs placebo (n=34) in outpatients who had an acute respiratory infection with cough,

using subjects' subjective scoring of daytime cough frequency and severity and nighttime cough severity and breathlessness, objective measurement of sputum quantity and subjective assessment of ease of expectoration. The results indicate DXM with salbutamol was more effective than the other two groups in suppressing nighttime cough. A significant improvement in symptom parameters was seen during the day for all treatment groups, and there were no significant differences between groups in symptom score for cough frequency or severity during the day, sputum quantity or ease of expectoration [Tukiainen 1986].

Parvez conducted 3 double-blind randomized placebo-controlled trials (n=108; n=134; n=209; total n=451) of a single dose of DXM 30 mg for acute cough due to acute upper respiratory infection. Objective quantitative evaluation with a multidimensional cough measurement system (recordings), and subjective patient assessments of cough and rating of troublesomeness of cough, consistently showed significantly reduced cough counts and total effort, with increased rest periods and unchanged average intensity per cough bout. Subjective assessments with VAS in 2 studies showed no treatment effects, but in the third study global assessment of cough showed a trend towards improvement with DXM at 120 minutes and the rating of cough troublesomeness showed DXM significantly superior at 120 minutes [Parvez 1996].

Lee studied DXM 30 mg (n=21) vs placebo (n=22) as a single dose for acute cough associated with URI, using objective recording of cough frequency (CF) and cough sound pressure level (CSPL), along with subjective patient assessments of cough severity. There was no significant difference from placebo for CF, CSPL and subjective scores. There was a statistically significant greater reduction in mean CSPL from baseline to 90 minutes with DXM, but not at 135 or 180 minutes [Lee 2000].

Pavesi performed a meta-analysis of 6 RCTs using a single 30 mg dose of DXM (n=356) or placebo (n=354) for acute cough due to uncomplicated URI, using objective recording continuously for 3 hours after treatment, measuring cough bouts, cough components, cough effort, cough intensity, and cough latency. The meta-analysis showed consistent results across most of the studies for each of the efficacy variables, with statistically significantly greater reductions vs placebo in

cough bouts (-12.7%), cough components (-13.4%), cough effort (-17.3%), and increase in cough latency (+17.3%) with DXM, but not for cough intensity (-5.8%) [Pavesi 2001].

3.3.1.4 Expectorants

A review of the literature found 3 RCTs of guaifenesin as a treatment of common cold symptoms in adults. One studied guaifenesin for cough, and this study was negative. The others evaluated guaifenesin as an expectorant, and it was found to be effective, thinning sputum and decreasing sputum volume, as well as decreasing cough frequency and intensity.

Robinson studied adults with moderate-to-severe cough associated with URI, treated with guaifenesin (GUA) 200 mg (n=118) or placebo (n=121) 4 times daily for 3 days. Subjective ratings by subjects and physician evaluation, along with objective measure of sputum characteristics found GUA significantly reduced cough frequency, cough intensity, and chest discomfort in subjects with initial nonproductive and productive cough and significantly increased sputum volume and facilitated raising sputum in subjects with initial productive cough [Robinson 1977].

Kuhn administered GUA 400 mg (n=33) or placebo (n=32) every 6 hours for 30 hours in subjects with cough associated with acute respiratory illness of < 48 hours duration. Using objective recorded cough counting and subjects' subjective ratings of cough, cough severity, cough discomfort, chest discomfort, sputum quantity, and thickness, the study revealed no antitussive effect, but GUA was associated with a perceived decrease in sputum quantity and a reduction in sputum thickness [Kuhn 1982].

Parvez compared GUA 1200 mg/day (n=31) to placebo (n=29) over 14 days in adult patients with chronic cough. GUA-treated patients maintained a steady sputum volume output over the study period with a significant difference to placebo of 37% on day 14. Fucose, a marker for sputum glycoprotein, was significantly reduced in the GUA compared to the placebo group on day 14. On a subjective scale for ease of expectoration, a subgroup of high sputum producers (>40mL pre-treatment) reported a large and significant improvement. GUA also produced

larger reductions in average intensity per cough compared to placebo on days 4 and 7 which was statistically significant on day 4 ($p<0.05$) [Parvez 1996].

3.3.1.5 Drug combinations

Seven published, randomized placebo-controlled trials of various combinations of AH/decongestant with or without DXM as multisymptom cold relievers were identified, and each study found efficacy vs placebo:

Berkowitz study of PSE 120 mg with loratadine 5 mg (n=142) vs placebo (n=141) in subjects with the common cold used physician assessment of overall response and evaluation of severity scores for rhinorrhea, nasal patency, and swelling on days 3 and 5, as well as subjects' subjective scoring of overall response and symptoms. Evaluations by both subjects and physicians suggest the PSE-loratadine combination is superior to placebo in relieving symptoms, including nasal congestion, sneezing, postnasal drainage (PND), and nasal discharge [Berkowitz 1989].

Blanco de la Mora compared 2 tablets of (PSE 60 mg with loratadine 2.5 mg and acetaminophen 500 mg) with placebo (total n=40) using investigator subjective assessment of nasal congestion, rhinorrhea, and general malaise on days 3 and 5, as well as subjects' subjective evaluation of symptoms. Significant difference between treatment groups was observed on day 3, and a favorable effect on edema of nasal mucosa and significant reduction of rhinorrhea were found on day 3 [Blanco de la Mora 2000].

Curley evaluated PSE 120 mg with dexbrompheniramine 6 mg (n=38) vs placebo (n=35) twice daily for 7 days in adults with common cold symptoms (present for 12 to 72 hours). Objective pulmonary function testing, and subjects' subjective daily assessments of severity of 17 symptoms for 14 days demonstrated reduced post-nasal drainage (PND) and significantly decreased severity of cough, nasal discharge, and throat clearing during first few days of treatment. Cough was 20 to 30% less prevalent in the active group than in the placebo group within 3 days of starting therapy. Active therapy demonstrated significantly lower mean severity rank of cough on days 3 to 5, of nasal discharge on day 2, of nasal obstruction on days 2 to 5 and of throat clearing on days 2 to 3 [Curley 1988].

Thackray used a double blind cross-over design with 70 subjects taking placebo vs a combination of DEX 15 mg with DOX 7.5 mg and ephedrine 8 mg and acetaminophen 600 mg, given in a single bedtime dose on 2 consecutive nights in subjects with the common cold. Subjects' subjective assessments of symptoms indicated cough improved significantly vs placebo, as did nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, and disturbed sleep. A significant number of active treatment subjects experienced global symptomatic relief compared with subjects on placebo [Thackray 1978].

Mizoguchi studied DEX 15 mg with DOX 7.5 mg and acetaminophen 600 mg and ephedrine 8 mg (n=224) vs placebo (n=208) in a single evening dose in subjects with common cold symptoms for 1 to 5 days who were experiencing at least moderate nasal congestion and runny nose, at least a mild cough, and at least mild pain with one or more of the following: sore throat, sore chest, headache, or body aches and pain. Subjects' subjective scoring of symptoms 3 hours post-dosing and 1 hour after rising the next morning found clinically and statistically significant relief vs placebo for the primary endpoint (composite of nasal congestion/runny nose/cough/pain relief scores 3 hours post-dosing). Each individual symptom score was also significantly improved at 3 hours, and there were clinically and statistically significant improvements on composite score and each individual symptom score the following morning [Mizoguchi 2007].

Galvez studied the common cold with associated cough, nasal congestion, and rhinorrhea, using DEX 20 mg with PSE 60 mg and azatadine 1 mg (n=28) or placebo (n=32) 3 times daily for 5 days. Subjective assessment of symptoms by a physician in consultation with subjects found more rapid and complete relief of nasal congestion and cough, excellent or good therapeutic response to treatment at interim and final evaluations in statistically greater number of subjects on active treatment, as well as faster onset of symptomatic relief (reported at 12 hours by 55% of treated vs 17% of placebo subjects; excellent or good overall therapeutic responses by day 3 in 60% of treated vs 8% of placebo group; and by day 5 in 77% of treated vs 21% placebo subjects [Galvez 1985].

Scavino gave DEX 20 mg with PSE 60 mg and azatadine 1 mg (n=29) or placebo (n=29) 3 times daily for 5 days to subjects with the common cold and associated cough. Physician assessment of signs and subjective assessment of symptoms (in consultation with subjects) revealed statistically significant greater reduction in

symptom severity scores at interim and final evaluations with treatment (59% improvement vs 33% on placebo at day 3; and 92% vs 69% on day 5), as well as faster onset of symptomatic relief (reported at 12 hours or less by 40% of treated subjects vs none on placebo); and more rapid improvement (lessened severity) in signs on treatment, a statistically significant difference (57% improvement vs 30% with placebo on day 3, and 93% vs 73% on day 5). Excellent or good overall therapeutic responses by day 3 for 76% of treated vs 17% of placebo group, and by day 5, 88% of treated vs 48% of placebo group [Scavino 1985].

The Cochrane Review of OTC medications for acute cough in adults and children evaluated the effect on cough of several classes of medications used to treat cough and cold. The review encompassed 24 RCTs (17 in adults and 7 in children) involving 2,876 adults and 516 children. Antitussives, expectorants, mucolytics, antihistamine/decongestant combinations and other drug combinations were evaluated. It was concluded that there is no good evidence for or against the effectiveness of OTC medicines in acute cough. Interestingly, the authors state that the results of their review have to be interpreted with caution due to differences in study designs, populations, interventions and outcomes between studies. The numbers of studies in each group were small, and studies often showed conflicting results. They concluded that the effect sizes in many studies were unclear, and questioned whether all of the positive results are clinically relevant.

The European Respiratory Society (ERS) guidelines on the assessment of cough notes that there is no standard approach for monitoring cough, and that in acute cough, there is a large placebo effect and considerable patient variability in response. Thus, “any parallel group study must be of a large size in order to convincingly show efficacy. Indeed, the only robust study demonstrating antitussive efficacy in acute cough is a meta-analysis of > 300 subjects.” (see above, Pavesi 2001) It is noteworthy that none of the individual studies cited above enrolled groups this large.

The American College of Chest Physicians (ACCP), in its Diagnosis and Management of Cough: Evidence-based Clinical Practice Guidelines, states, “Patients with acute cough (as well as PND [post-nasal drainage] and throat clearing) associated with the common cold can be treated with a first-generation A/D combination (brompheniramine and sustained-release pseudoephedrine)” [Irwin 2006].

CHPA concludes that these clinical trials in adults support the symptomatic benefits of cough and cold medications.

3.3.2 Pediatric Efficacy Data

Few pediatric trials met the enrollment criteria for adequately powered randomized controlled trials. The number of placebo-controlled RCTs is rather small. Inconsistent results observed for published pediatric studies in this area may be attributed in large part to the lack of sensitive and specific methodology with which to evaluate primarily subjective symptomatology. This is particularly compounded in the pediatric population, where children may have limited expressive capabilities and ability to respond regarding subjective symptoms in a consistent fashion, as well as variable levels of cooperation. Another limitation of certain studies is that some of the endpoints selected for study (e.g., appetite, crankiness, vomiting) were not appropriate for the mechanism of action of the test medications.

An important factor potentially contributing to the inconsistent results found in pediatric clinical trials in the literature is that most studies were underpowered. To test this hypothesis, a *post hoc* statistical analysis of 8 pediatric clinical trials was performed (see Appendix 2). It was found that, indeed, 7 of the 8 studies were vastly underpowered to show statistically significant differences based on the actual treatment effect observed. Each study would have required several hundred subjects per treatment arm, as opposed to the several dozen actually enrolled, in order to achieve statistical significance based on the observed magnitude of treatment effect.

3.3.2.1 Antihistamines

Sakchainanont conducted a study of antihistamines in children 1.5 months to 60 months of age with rhinorrhea with or without non-productive cough of 3 days duration. Subjective evaluations of nasal discharge, nasal turbinate edema, and cough were done, comparing CHLOR 0.35 mg/kg/day given 3 times daily (n=48) dose or clemastine fumarate 0.05 mg/kg/day in divided dose twice daily (n=48) or placebo 2 to 3 times daily (n=47) for 3 days. Study drugs were prepared in equal volumes to facilitate blinding. There was statistically significant improvement of every symptom in every group; only the character of nasal discharge was different,

with clemastine statistically significant vs placebo, while CHLOR was nearly statistically significant vs placebo. There was no difference between the 2 active groups. Slight drowsiness and sleepiness were the side effects evaluated, and these were not different from the placebo group [Sakchainanont 1990].

Paul enrolled 100 children aged 2 to 16.5 years (median 4.5 years) with nocturnal cough associated with URI. Patients were stratified by ages 2 to 5 years, 6 to 11 years, and 12 to 18 years of age, and given diphenhydramine (DPH) 1.25 mg/kg of body weight (n= 33) or placebo (n=34) as a single dose 30 minutes before bedtime. The remaining 33 children were randomized to receive DXM (see Antitussives section below). Parents made subjective assessments of frequency, severity and bothersome nature of nocturnal cough, and of sleep quality for children and parents. There were no significant differences between treatment groups, although a trend for better sleep quality was noted for the DPH group [Paul 2004].

Yoder studied a subset of the Paul subjects. Children 6 to 18 years of age (median age 7.5 years) with nocturnal cough related to URI, who were treated for 2 days with DPH 1.25 mg/kg/dose (n=12) or placebo (n=13) at bedtime, were evaluated using the children's self-assessment of cough relief and sleep quality. There were no significant differences between treatment groups, but a trend for better sleep quality in the DPH group was noted [Yoder 2006].

3.3.2.2 Decongestants

Martinez-Gallardo enrolled 65 children with common colds, age 2 to16 years in a RCT of PSE alone (n=15) or in combination with naproxen (NAP) (n=20), placebo for PSE (n=14) or placebo for the combination (n=16) for 5 days. The dose of each component escalated with each age group (2 to 5 years PSE 15 mg with or without NAP 50 mg; 6 to 9 years PSE 30 mg with or without NAP 100 mg; 10 to 12 years PSE 45 mg with or without NAP 150 mg; and 13 to 16 years PSE 60 mg with or without NAP 200 mg). The physician evaluated cold signs and symptoms after 3 and 5 days, and reported significantly shorter duration of nasal obstruction, mucosal edema, lacrimation, and headache with the combination. Greater symptom relief was reported on the 3rd and 5th days with the combination compared with the other groups, between which there were no differences [Martinez-Gallardo 1994].

3.3.2.3 Antitussives

In the above study by Paul, 33 subjects were randomized to receive DXM rather than DPH. Children age 2 to 5 years received DXM 7.5 mg, 6 to 11 year olds received 15 mg, and 30 mg was given to those more than 11 years of age. Subjective assessments of cough by parents showed improvement for all outcomes for all groups, with no statistical difference between groups in providing nocturnal symptom relief.

In the Yoder study described above (subset of the Paul study), children age 6.2 years to 16.5 years (median age 7.5 years) were randomized to receive DXM (n=12) or placebo (n=13) in the same fashion as in the Paul study. There were no significant differences from placebo regarding symptom relief [Yoder 2006].

3.3.2.4 Expectorants

No published single-ingredient RCTs of patients with the common cold were identified.

3.3.2.5 Combination products

Taylor conducted a RCT of nocturnal cough of less than 14 days' duration in 2 cohorts: children aged 18 months to 5 years (mean age 4.7 years) received either GUA 50 mg with DXM 7.5 mg, or GUA 50 mg with codeine 5 mg, or placebo; children aged 6 to 12 years received GUA 100 mg with DXM 15 mg, or GUA 100 mg with codeine 10 mg, or placebo (total n for GUA with DXM = 19; total n for GUA with codeine = 17; placebo n = 13). Parents provided subjective morning assessments of cough and sleep. Neither combination was superior to placebo in treating nocturnal cough at the doses given in either age group [Taylor 1993].

Hutton enrolled children age 0.5 to 5 years (mean age 25 months) with signs of URI. This RCT evaluated a combination of BROM 4 mg/5 ml with PE 5mg/ml and phenylpropanolamine (PPA) 5 mg/5 ml (n=36) or placebo (n=27) given 3 times daily so that the BROM dosage was 0.5 to 0.75 mg/kg/day for 2 days. Parents' subjective assessments of symptoms (congested or runny nose, breathing trouble, fever, cough, decreased appetite, crankiness, sleep disturbance, and excessive sleepiness) were performed at 48 hours. There were no differences from placebo in individual or composite symptom score changes [Hutton 1991].

Clemens enrolled children aged 0.5 to 5 years with acute (<7 days) URI, who received placebo (n=31) or BROM 2 mg/5 ml with PPA 12.5 mg/ml (n=28): 0.5 teaspoon for age 6 months to 2 years, and 1 teaspoon for ages 2 to 5 years, no more often than every 4 hours and no more than 4 doses, for 48 hours. Parents made subjective assessments 2 hours after each dose, of changes in symptoms (runny nose, nasal congestion, and cough) and whether the child was sleeping. No statistically significant differences in symptom improvement were observed between groups, but a higher proportion of treated children were sleeping 2 hours after a dosage of active medication (46.6% vs 26.5%) and this difference was statistically significant [Clemens 1997].

Reece evaluated cough in children age 2 months to 12 years when treated with placebo or 1 of 2 combination products: A (each 5 ml contained PPA 12.5 mg with pheniramine 6.25 mg and DXM 15 mg and ammonium chloride 90mg) or B (each 5 ml contained DXM 7.5mg with PPA 8.75 mg and glyceryl guaiacolate 37.5 mg and alcohol 5%). Each of these was dosed according to an age chart that provided dosing for <2 years, 2 to 6 years, and 7 to 12 years. There was an inpatient cohort (n=22; ages 2 months to 9 years; average age 1.9 years) that employed a tape recording for cough counts, and an outpatient cohort (n=43; age 2 months to 12 years; average age 3.6 years) that relied on parental assessment of cough. The authors stated that in the inpatient study the superiority of the antitussive medications was so obvious that statistical analysis was not necessary (the data in the paper have now been analyzed by a statistician and found not to be statistically significant). The outpatient study did not demonstrate significant differences in treatments [Reece 1966].

Korppi enrolled 50 children age 1 year to 10 years (mean age 3.8 years) with cough associated with URI in a RCT comparing DXM 1.5mg/ml (n=24) with or without salbutamol 0.2 mg/ml vs placebo (n=26). Subjects age < 7 years received 5 ml, subjects ≥ 7 years received 10 ml, 3 times daily for 3 days. Parents' subjective assessments of symptoms and daily assessment of general condition revealed that symptom scores dropped significantly in all groups, but there was no difference between groups, neither for symptom scores nor in reported general condition on any of the 3 days [Korppi 1991].

In addition to the reviews of cough and cold preparations described previously which included comments regarding pediatric use, the American Academy of Pediatrics (AAP) Committee on Drugs has commented on the use of dextromethorphan-containing cough remedies in children. This statement regarding the treatment of cough is apparently the only cough and cold medication on which AAP offers an opinion. AAP concluded that no well-controlled studies support the efficacy and safety of these products for the treatment of cough in children, and note that dosing is derived from extrapolation of adult data. The Committee on Drugs calls for further research of these preparations in children.

3.4 Summary Points

- Evidence for the efficacy and safety of OTC cough and cold medicines based on randomized, placebo-controlled trials in adults are prevalent in the literature.
- The results of pediatric studies of OTC cough and cold medicines have been inconclusive to date.
    - There are considerable challenges and limitations to the study of cough and cold medicines in pediatrics related to study design and lack of sensitive, relevant endpoints.
    - The majority of pediatric randomized, controlled trials have been underpowered.
    - Recommendations by professional, authoritative bodies to not use certain ingredients in young children relate, for the most part, to the lack of robust clinical trial data in this patient population.
- CHPA concludes that it would be beneficial to expand the body of evidence for the use of cough and cold medicines in children.
    - Studies must be appropriately powered to achieve statistical significance.
    - Appropriate efficacy endpoints based on the mechanism of action of the test medications must be employed.
    - The field will be advanced by the development of robust, validated methodology for evaluating the signs and symptoms of the common cold.

4 EXTRAPOLATION OF PHARMACOKINETIC DATA TO DETERMINE APPROPRIATE DOSING IN CHILDREN

4.1 Key Points

- Traditionally, pediatric doses, including those for OTC monograph drugs, were based on age-weight rules. Extrapolation with pharmacokinetic data is currently used to select pediatric doses, along with safety information in children. Where available, pharmacodynamic and/or efficacy data are also used to select doses.
- Pediatric and adult pharmacokinetics (clearance, half-life, and/or distribution volume) do not need to be the same to extrapolate pediatric doses that would correspond with adult efficacy. Instead, data are used to select doses that provide comparable blood levels as adults, expressed as total and maximum drug exposure (AUC_{INF} and C_{MAX}).
- Available pediatric pharmacokinetic data for pseudoephedrine and chlorpheniramine confirm the appropriateness of recommended OTC monograph doses for children 2 to <12 years, and 6 to < 12 years, respectively.
- Member companies of CHPA are committed to obtain additional pharmacokinetic data for other OTC cough and cold drugs, where needed, to better characterize and confirm dosing in children.

This section provides an overview of pediatric dosing from early years when doses were based on general age-weight rules without an understanding of drug disposition in children. Such rules formed the basis of recommended pediatric doses of OTC cough and cold drugs in the 1976 monograph review. Because of the evolution of pediatric clinical research through the 1990s, pharmacokinetic studies in children are more common, and the data are used to determine appropriate doses. A sufficient amount of pharmacokinetic data is available in children and adults for two OTC cold drugs with which to show a relationship between dose and drug exposure. The findings across studies and age groups are included in this section, whereas listings of the data are located in Appendix 3.

4.2 Dosing by Pediatric Age Group

Historically, adult doses provide the reference point for therapy in children with adjustment for body size. The age and body weight or surface area of children were used to adjust adult doses. For example, Clark's weight rule was often used to approximate dose by dividing the child's weight in pounds by 150 (or weight in kilograms by 70), and multiplying

the result by the adult dose [Munzenberger 1980]. By contrast, the majority of chemotherapy regimens and trials specify doses of cytotoxic drugs normalized to body surface area in m^2 [Sharkey 2001]. However, estimation of body surface area in pediatric patients is particularly problematic, as conventional nomograms require accurate determination of both height and weight.

Doses of pharmacologically active agents in children are generally provided by age group. The 1994 Pediatric FDA Final Rule [59 FR 64240], as well as current guidelines [ICH E11 2000] on clinical investigations of drugs in pediatric populations consider the following groups:

- Term newborn infants (0 to 27 days)
- Infants and toddlers (1 month to < 2 years)
- Children (2 to < 12 years)
- Adolescents (12 to 16 or 18 years)

These age groups generally reflect developmental stages – changes after birth; early growth spurt; gradual growth from 2 to <12 years; and pubertal and adolescent growth spurt and development towards adult maturity. Although not necessarily related to clinical differences, the age group 2 to < 12 years, is sometimes further subdivided in terms of the child's ability to accept and use different pharmaceutical dosage forms: pre-school children (2 to < 6 years) and school children (6 to < 12 years).

4.3 Basis for Pediatric Dosing in the OTC Cough and Cold Monograph

The 1976 FDA Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products discussed the best approach to pediatric dosage [41 FR 38312]. The panel concluded, "the dosage that will produce optimum therapeutic effects in a particular patient, adult or child, is dependent upon factors such as the drug itself, individual patient variables such as special sensitivity or tolerance to the specific agent, age, weight, and metabolic, pathological, or psychological conditions. Children's dosage calculated by any method that does not take all of these variables into account, therefore, can only be considered general guides" [41 FR 38333].

The panel also commented that dosing based on the "age of the child, although convenient, may be the least reliable method because of the large variation in the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the panel concluded that dosage recommendations based on age are the most reasonable since they would be most easily understood by the consumer" [41 FR 38333].

After consultation with a group of experts in pediatric drug therapy, the Panel recommended the following pediatric doses based on weight and age: “For infants under 2 years of age, the pediatric dosage should be established by a physician. For children 2 to under 6 years of age, the pediatric dosage is ¼ the adults dosage; for children 6 to under 12 years of age, the dosage is ½ the adult dosage” [FR 41176 p 38333]. This dosing pattern generally follows Clark’s weight rule, which is illustrated in Table 4.1 for three cough and cold drugs.

Table 4.1 Pediatric Single Doses for OTC Drugs in the Cold/Cough Monograph

	12 to adults	**6 to < 12 y**	**2 to < 6 y**	**Under 2 y**
Weight Range (lb)	-----	48 to 95	24 to 47	< 24
Mean Weight (lb)	150	71.5	35.5	12
Clark’s Weight Rule	150/150 = 1	71.5/150 = 0.48	35.5/150 = 0.24	12/150 = 0.08
Monograph Dose	1	½	¼	Consult a doctor
Examples				
Pseudoephedrine	60 mg	30 mg	15 mg	Consult a doctor
Chlorpheniramine	4 mg	2 mg	Consult a doctor	Consult a doctor
Dextromethorphan	30 mg	15 mg	7.5 mg	Consult a doctor

4.4 Drug-Exposure Basis of Pediatric Dosing: The Current Method

More recently, pharmacokinetic studies in children, including infants and toddlers, have increased our understanding of drug disposition in this population. These data are used to select pediatric doses that provide blood levels similar to those observed in adults [ICH E11 2000]. Pediatric safety data are also considered in the selection of pediatric doses, and where possible, either pharmacodynamic and/or efficacy data are considered as well.

Extrapolation from adult efficacy to children may be appropriate for some therapeutic classes of drug, and examples include prescription antihistamines for allergic rhinitis and proton pump inhibitors for gastrointestinal reflux disease[1]. The basis for extrapolation (per the approved product labeling[2]) is “the likelihood that the disease course, pathophysiology, and the drug’s effect are substantially similar to that of adults”. Recommended doses of these products for pediatric populations are then based on cross-study comparisons of pharmacokinetic data in adults and children and on the drug’s safety data profile in the

[1] www.fda.gov/cder/pediatric/labelchange.htm, Prea_label_post-mar_2_mtg.htm, Summaryreview.htm, Accessed September 5, 2007

[2] Allegra®, Claritin®, Clarinex®, Zytec®, and Xytal®

various age groups. Although drug clearances may differ, recommended doses are usually those that provide comparable total (AUC_{INF}) and maximum drug exposure (C_{MAX}) among different age groups.

4.5 Recommended Doses for Pediatric OTC Products Requiring Preapproval by FDA

Two or more monograph ingredients may be combined into a cough and cold product formulation and be marketed without preapproval by FDA. However, preapproval is required if one of the OTC drugs is regulated under a New Drug Application (NDA). Three pediatric cold (NDA 21-128; 21-373) and allergy-sinus (NDA 21-587) combination OTC products required additional clinical studies for approval. Pseudoephedrine, with and without chlorpheniramine, in combination with ibuprofen, had to follow *de facto* the NDA process, as ibuprofen is an NDA drug.

The pediatric information requested by FDA was pediatric pharmacokinetic data on the active ingredients in the target population to assess potential drug interactions and doses. In addition, open-label safety studies in children were requested for the combination of cold and allergy drugs with ibuprofen because there was no history of combined use in the pediatric population. The objective of these safety studies was to characterize the adverse event profile of the proposed OTC combination products. Table 4.2 summarizes the pediatric clinical programs for each drug application.

The selection of pediatric doses for children from 2 to < 12 years was not straightforward because ibuprofen and pseudoephedrine have a different number of weight-age divisions for dosing. OTC analgesics have more divisions than OTC cough and cold medications, which decrease the differences between the minimum and maximum doses within each pediatric age group (2 to < 6 years and 6 to < 12 years). The sponsor of NDA 21-128 dosed the children by mg/kg in the pharmacokinetic and open-label safety studies, and proposed the dosing schedule associated with ibuprofen summarized in Table 4.3. The dosing schedule associated with pediatric OTC cough and cold medications with fewer weight-age divisions was approved for the combination product based on the upper limit of doses permitted by the monograph in each age group. There were no pharmacokinetic interactions between active ingredients tested, and the overall safety profile was consistent with each individual ingredient's established adverse event profile. The approved dosing schedule is summarized in Table 4.4.

Table 4.2 Pediatric Information Submitted in Three NDAs for OTC Combination Cold/Allergy/Sinus Products

NDA	Drug Product	Indication and Pediatric Clinical Program
21-128	IBU 100 mg; PSE 15 mg per 5 mL suspension ***Dosing Chart*:** Under 2 years — Ask a Doctor 2 to 5 years — 1 tsp 6 to 11 years — 2 tsp	***Indication:*** Temporarily relieves these cold, sinus, and flu symptoms: • nasal and sinus congestion • stuffy nose • minor body aches and pains • headache • fever • sore throat ***Pediatric Clinical Program*** • Multiple-dose pediatric pharmacokinetic study in healthy children, ages 4 to 11 years (n=24) • Safety study in children with symptomatic rhinitis, ages 2 to 11 years (n=114)
21-373	IBU 100 mg; PSE 15 mg per 5 mL suspension ***Dosing Chart*:** Under 2 years — Ask a Doctor 2 to 5 years — 1 tsp 6 to 11 years — 2 tsp	***Indication:*** Temporarily relieves these cold, sinus, and flu symptoms: • nasal and sinus congestion • stuffy nose • minor body aches and pains • headache • fever • sore throat ***Pediatric Clinical Program*** • Single-dose pediatric pharmacokinetic study in children ages 2 to 5 years (n=23) • Single-dose pediatric pharmacokinetic study in healthy children, ages 6 to 11 years (n=31) • Safety study in children with symptomatic rhinitis or sinusitis, ages 2 to 11 years (n=106)
21-587	IBU 100 mg; PSE 15 mg; CPM 1 mg per 5 mL suspension ***Dosing Chart*:** Under 6 years — Ask a Doctor 6 to 11 years — 2 tsp	***Indication:*** For the temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold: • runny nose • itching of the nose and throat • sneezing • sinus pressure • minor body aches and pains • nasal congestion • headache • fever ***Pediatric Clinical Program*** • Single-dose pediatric pharmacokinetic study in children with allergic rhinitis, ages 6 to 11 years (n=30) • Safety study in children with upper respiratory allergies, ages 6 to 11 years (n=111)

Key: CPM – chlorpheniramine maleate, IBU – ibuprofen, PSE – pseudoephedrine HCl

Table 4.3 Dosing Schedule Proposed for the Ibuprofen-Pseudoephedrine Suspension, 100-5 mg/5 mL (NDA 21-128)

Weight Range (lb)	Age (years)	Dose[a] (teaspoon)	Ibuprofen Dose (mg)	Pseudoephedrine HCl Dose (mg)
Under 24	Under 2	Consult Doctor	Consult Doctor	Consult Doctor
24 - 35	2 - 3	1	100	15
36 - 47	4 - 5	1 ½	150	22.5
48 - 59	6 - 8	2	200	30
60 - 71	9 - 10	2 ½	250	37.5
72 - 95	11	3	300	45

a: Dosage may be repeated every six to eight hours, but not more than four times a day.

Table 4.4 Approved Dosing Schedule for NDAs 21-128 and 21-373

Weight Range (lb)	Age (years)	Dose[a] (teaspoon)	Ibuprofen Dose (mg)	Pseudoephedrine HCl Dose (mg)
Under 24	Under 2	Consult Doctor	Consult Doctor	Consult Doctor
24 - 47	2 - 5	1	100	15
48 - 95	6 - 11	2	200	30

a: Dosage may be repeated every six hours, but not more than four times a day.

Subsequently, the dosing schedules for the two other pediatric OTC combination products (NDA 21-373 and 21-587) were based on these dosing schedules for the cold and allergy drugs with fewer weight-age breaks than analgesics, and on the upper limit of doses in the monograph. For the triple combination suspension (ibuprofen-pseudoephedrine-chlorpheniramine), efficacy in children ages 6 to < 12 years at the approved doses was extrapolated from adult efficacy demonstrated with the adult combination product (NDA 21-441). In addition, there were no pharmacokinetic interactions among the three drugs in children, and the safety profile was consistent with each individual drug's adverse event profile.

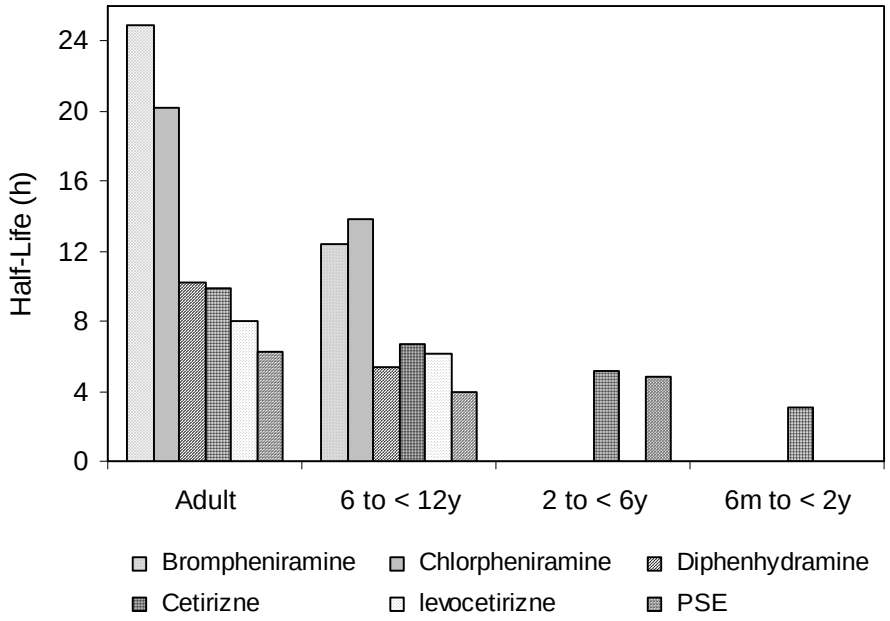
4.6 Insights From Available Pediatric Pharmacokinetic Data for OTC Drugs

Pediatric pharmacokinetic data are available for orally administered pseudoephedrine [McNeil 1999, Auritt 1981, Simons 1996, Wyeth 2002a, Wyeth 2004], chlorpheniramine [Wyeth 2004, Simons 1982], brompheniramine [Simons 1999], and diphenhydramine

[Simons 1990] in children ages 6 to < 12 years. Data for pseudoephedrine are also available in children ages 2 to < 6 years [McNeil 1999, Wyeth 2002a]. Compared with adults, weight-adjusted oral clearances are higher and half-lives are shorter in children, which is generally true for many drugs, although there are exceptions.

A comparison of mean values of half-life is shown in Figure 4.1. Estimates of half-life are used to determine dose intervals, time to steady state, and drug accumulation in the blood with multiple dosing. Because dosing intervals for OTC drugs are generally the same for adults and children, the shorter half-lives indicate that steady state would be reached in shorter times and that there would be less drug accumulation in children.

Figure 4.1 Cross-Study Comparison of Mean Half-Lives for OTC Drugs and Two Prescription Antihistamines



Urine metabolite data in older children have been published for pseudoephedrine [Simons 1996] and chlorpheniramine [Simons 1983]. Elimination of pseudoephedrine is primarily through the renal route, with about 75% of an administered dose excreted unchanged in urine by adults [Nieder 1988]. In one pharmacokinetic study in children, urine was collected from two subjects receiving 30 mg pseudoephedrine. The recovery of unchanged drug over 24 hours is comparable with adults at 66% of the dose [Simons 1996].

Chlorpheniramine is rapidly metabolized by the liver to mono and di-demethylated metabolites, and to polar oxidative metabolites. A role of cytochrome P450 2D6 has been

shown in the metabolism of chlorpheniramine. After a single-dose of chlorpheniramine in 11 children, the recovery of drug and metabolites over 48 hours was 11.3 ± 6.7% chlorpheniramine, 23.3 ± 11.1% demethylchlorpheniramine, and 9.6 ± 9.4% di-demethyl-chlorpheniramine [Simons 1983]. The relative percents of each species excreted are consistent with those in adults. However, the absolute percents are about double those in adults, which most likely reflect the incomplete 24-hour collection of urine in adults [Kabasakalian 1968].

Urine metabolite data in neonates and infants up to 12 months of age have recently been published for dextromethorphan [Blake 2007]. The data indicate that cytochrome P450 2D6 activity is detectable and concordant with genotype by two weeks of age, shows no relationship with gestational age, and does not change with post natal age up to 12 months. In contrast, dextromethorphan N-demethylation developed more slowly over the first year of life. However, the pharmacokinetic and clinical relevance of this finding is unknown and would need further investigation.

4.7 Confirmation of Current OTC Pseudoephedrine Doses in Children, Ages 2 to < 12 Years

Pediatric and adult pharmacokinetics (clearance, half-life, and/or distribution volume) do not need to be the same to extrapolate pediatric doses that would correspond to adult efficacy. Instead, data are used to select doses that provide comparable blood levels as adults, expressed as total and maximum drug exposure (AUC_{INF} and C_{MAX}, respectively). In this section, pediatric pharmacokinetic data are used to confirm the appropriateness of recommended OTC pseudoephedrine doses in children that were originally based on Clark's weight rule.

4.7.1 Indication and Mechanism of Action

Oral pseudoephedrine is indicated for the temporary relief of nasal congestion, a prominent symptom of the common cold. It causes vasoconstriction by activating the postsynaptic α-adrenergic receptors indirectly through the displacement of norepinephrine [Hoffman 2001]. Targeted adrenergic receptors are located on the muscles lining the walls of blood vessels in the nasal passages. When activated by pseudoephedrine, the muscles contract, causing blood vessels to constrict. These constricted blood vessels allow less fluid to enter the nose, throat, and sinus linings, which result in decreased inflammation of nasal membranes as well as decreased mucous production [Empey 1981]. Thus, by constriction of blood

vessels, mainly those located in the nasal passages, pseudoephedrine causes a decrease in the symptoms of nasal congestion.

4.7.2 Available Pseudoephedrine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for pseudoephedrine in 119 children ages 2 through 11 years old were collected from a multiple-dose study [McNeil 1999], two published single-dose studies [Auritt 1981, Simons 1996], and three single-dose studies for pediatric cold and allergy-sinus OTC products [Wyeth 2002a, Wyeth 2004]. FDA summarized data for the latter studies as part of the basis of approval for new drug applications, NDA 21-373 and 21-587, and these summaries are publicly available per the Freedom of Information Act. The dose-independent pharmacokinetic parameters, oral clearance (CL/F), half-life ($t_{½}$), and apparent distribution volume (Vd/F) from studies in children and adults are listed in Table 4.5, which is located in Appendix 3. A listing of administered doses and drug exposure parameters (AUC_{INF} and C_{MAX}) is also located in Appendix 3 as Table 4.6.

For a cross-study comparison, three graphs of maximum pseudoephedrine exposure by dose for children ages 2 to < 6 years and 6 to < 12 years, and for adults are shown in Figure 4.2. The relationship between mean C_{MAX} values and dose is linear in each group, although the slopes are different. A horizontal dashed line is drawn across the figure at the point where a vertical line is drawn up from the 60-mg adult dose. This horizontal line intersects the slope for each children's group, which shows that the recommended pediatric OTC doses of 15 and 30 mg pseudoephedrine provide maximum concentrations comparable to that for a 60-mg dose in adults.

Mean values for total systemic exposure (AUC_{INF}) among age groups and studies are plotted by dose in Figure 4.3. Again, the relationship between mean AUC_{INF} values and dose is linear in each group, although the slopes are different. This graphical representation shows that the overall mean AUC_{INF} of the 30-mg dose in older children is comparable to adults (only about 14% lower). For the younger children, ages 2 to < 6 years, the overall mean AUC_{INF} is about 34% lower than that in adults. These differences reflect the higher, weight-adjusted clearances of pseudoephedrine in children. Yet, importantly, the average values for younger and older children fall between the total systemic exposures for the 30- and 60-mg doses in adults, which are both effective doses.

Figure 4.2 Means of Maximum Systemic Exposure by Single Pseudoephedrine Dose in Children and Adults

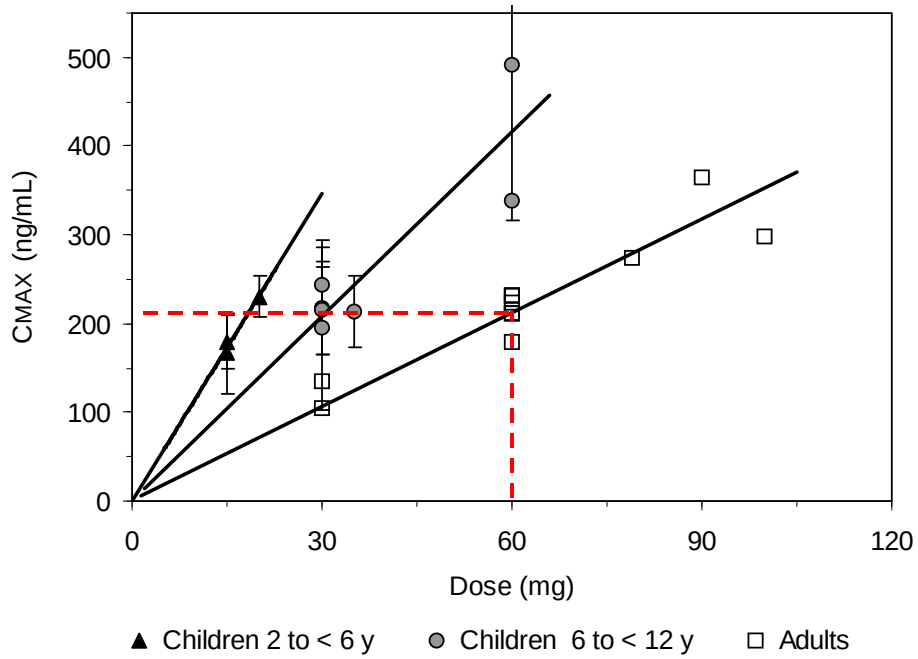
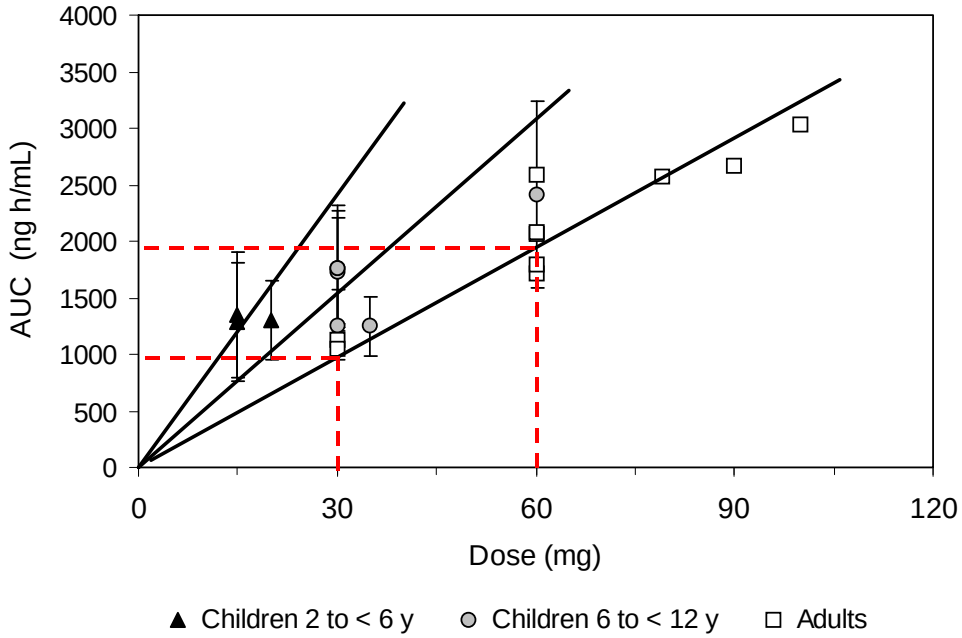


Figure 4.3 Means of Total Systemic Exposure by Single Pseudoephedrine Dose in Children and Adults



Pseudoephedrine 60 mg was found to be a generally recognized safe and effective medication for OTC use as an oral nasal decongestant by FDA's Review Panel based on a series of clinical studies [FR 41176]. One placebo-controlled study, which included an objective measure, showed the 30-mg dose having a significant decrease in resistance to flow in nasal congestion. A 30-mg dose of pseudoephedrine, when combined with ibuprofen 200 mg and/or chlorpheniramine 2 mg, has been shown to be effective in at least two out of three double-blind, placebo-controlled clinical trials [McNeil 1991, Meltzer 2004]. Results of these studies on assessment of relief of nasal symptoms are summarized in Table 4.5.

Table 4.5 Additional Supporting Efficacy for a 30-mg Pseudoephedrine Dose in Adults

Study (Clinical Model)	Design	Treatments	Nasal Symptom Endpoints	Results
McNeil 1991 Study 86-683 (sinus headache)	DB, PC, DR, PL, SD, MC (n=348)	I400/P60 I200/P30 Pbo	For all four summary measures of sinus congestion: SCID, MAXCID, TOTCOR, MAXCOR	I400/P60 = I200/P30 > Pbo
Meltzer 2004 (seasonal allergic rhinitis)	DB, PC, DR, PL, MD, MC (n=1044)	I400/P60/C4 I200/P30/C2 P30/C2 Pbo	OATSS and OATASS	I400/P60/C4 = I200/P30/C2 I400/P60/C4 > Pbo I200/P30/C2 > Pbo P30/C2 > Pbo I200/P30/C2 > P30/C2

Key: C - chlorpheniramine, DB – double blind, DR – dose response, I – ibuprofen, P - pseudoephedrine, Pbo – placebo, PC – placebo control, PL – parallel group, MC – multiple centers, MD – multiple dose, SD – single dose.

Nasal Symptom Endpoints:

Sinus congestion: SCID – sinus congestion intensity difference, MAXCID – maximum congestion intensity difference, TOTCOR – total congestion relief, and MAXCOR – maximum congestion relief.

OATSS – Overall average total symptom score: nasal congestion, sneezing, rhinorrhea, itchy nose/throat/palate, itchy/watery/red eyes, and pain.

OATASS - Overall average total antihistamine symptom score: sneezing, rhinorrhea, itchy nose/throat/palate, itchy/watery/red eyes

4.8 Confirmation of Current OTC Chlorpheniramine Doses in Children, Ages 6 to < 12 Years

Pediatric and adult pharmacokinetics (clearance, half-life, and/or distribution volume) do not need to be the same to extrapolate pediatric doses that would correspond to adult efficacy. Instead, data are used to select doses that provide comparable blood levels as adults, expressed as total and maximum drug exposure (AUC_{INF} and C_{MAX}, respectively). In this section, pediatric pharmacokinetic data are used to confirm the appropriateness of the recommended OTC chlorpheniramine dose in children that was originally based on Clark's weight rule.

4.8.1 Indication and Mechanism of Action

Chlorpheniramine is indicated to alleviate rhinorrhea and sneezing due to the common cold. The mechanism by which first-generation antihistamines reduce nasal discharge due to the common cold is believed to occur through anticholinergic effects. The main control of nasal secretion is autonomic (cholinergic), with parasympathetic stimulation increasing secretion [Lund 1996].

4.8.2 Available Chlorpheniramine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for chlorpheniramine in 41 children ages 6 through 11 years old were collected from a published study [Simons 1982] and a study submitted to FDA to support approval of a pediatric triple ingredient OTC product [Wyeth 2004]. FDA had summarized data for the latter study as part of the basis of approval, and this summary is publicly available. The dose-independent pharmacokinetic parameters, oral clearance (CL/F), half-life ($t_{½}$), and apparent distribution volume (Vd/F) from studies in children and adults are listed in Table 4.7, which is located in Appendix 3. A listing of administered doses and drug exposure parameters (AUC_{INF} and C_{MAX}) is also located in Appendix 3 as Table 4.8.

For a cross-study comparison, two graphs of maximum chlorpheniramine exposure by dose for children ages 6 to < 12 years and for adults are shown in Figure 4.4. The relationship between mean C_{MAX} values and dose is linear in each group, although the slopes are different. A horizontal, dashed line is drawn across the figure at the point where a vertical line is drawn up from the 4-mg adult dose. This horizontal line intersects the slope for the children's group, which shows that the current pediatric OTC dose of 2 mg chlorpheniramine provides maximum concentrations comparable to that for a 4-mg dose in adults.

Mean values for total systemic exposure (AUC_{INF}) among age groups and studies are plotted by dose in Figure 4.5. Mean AUC_{INF} for the 2-mg chlorpheniramine dose in children, ages 6 to < 12 years, is about 21% lower than the overall mean across studies for the 4-mg dose in adults. This difference reflects the higher, weight-adjusted clearance of chlorpheniramine in children. Yet, the mean value for children falls within the range of total systemic exposures for 2- and 4-mg doses in adults. Although the 2-mg chlorpheniramine dose has not been commonly studied in adults, evidence of efficacy versus placebo has been recently published for this dose when combined with 30 mg of pseudoephedrine [Meltzer 2004].

Figure 4.4 Means of Maximum Systemic Exposure by Single Chlorpheniramine Dose in Children and Adults

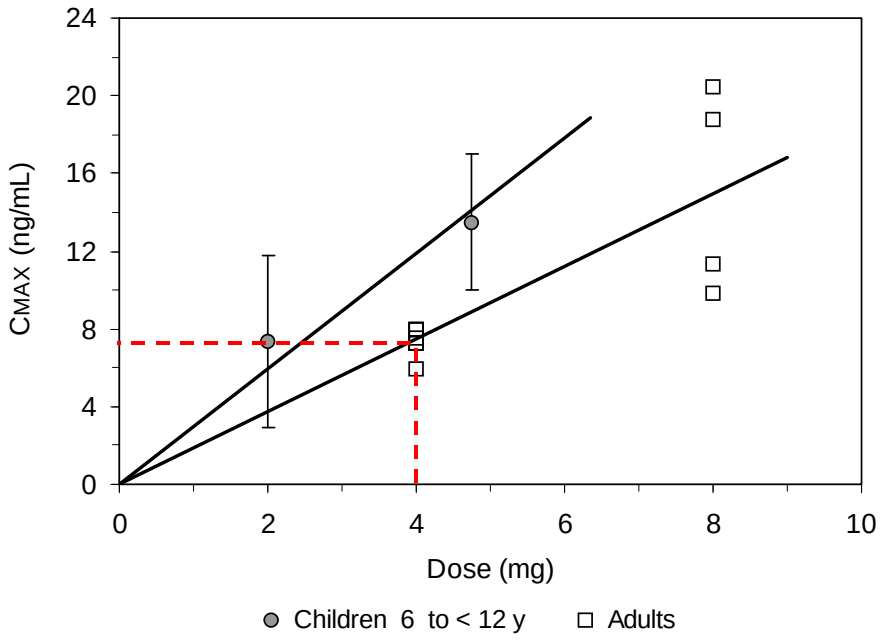
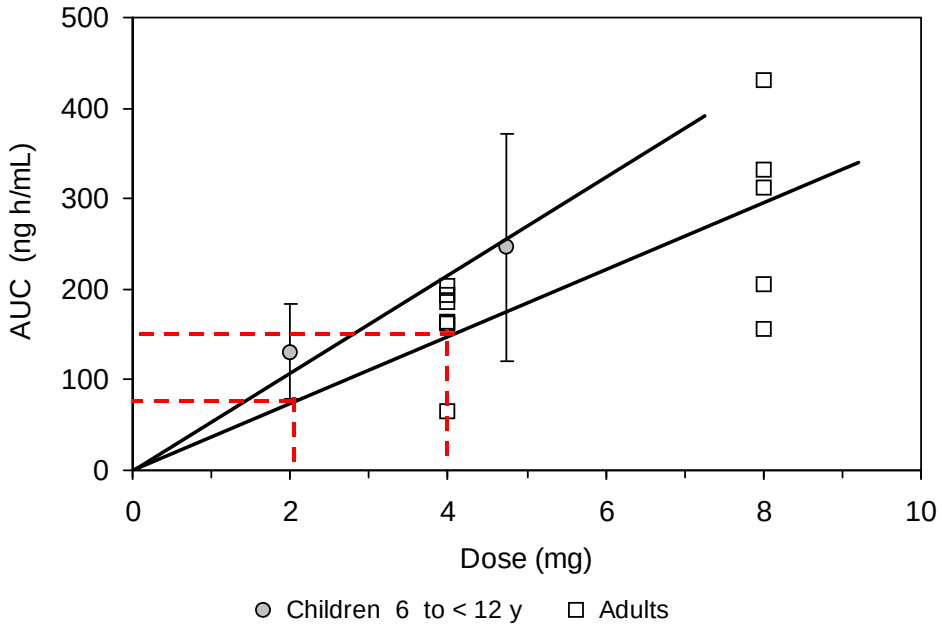


Figure 4.5 Means of Total Systemic Exposure by Single Chlorpheniramine Dose in Children and Adults



4.9 Summary

Cross-study comparisons of pediatric and adult, single-dose pharmacokinetic data indicate that recommended OTC pediatric doses for pseudoephedrine and chlorpheniramine provide comparable maximum drug exposures to those in adults. Total systemic exposures were within ranges of those from effective adult single doses. In practice, multiple doses of OTC cough and cold medications are administered such that average blood concentrations of ingredients would be somewhat higher, depending on the drug's half-life and dosing interval. Likewise, maximum exposure after multiple doses would be higher, although there is less accumulation in children due to the drugs' shorter half-lives.

Every drug has unique properties that may potentially affect its disposition differently in children and adults. As such, pediatric pharmacokinetic data are needed to assess doses for other OTC drugs by age group. CHPA member companies are committed to conducting pharmacokinetic studies in children 2 to < 12 years of age for the following ingredients: dextromethorphan, phenylephrine, guaifenesin, brompheniramine, diphenhydramine, and doxylamine. As shown in this section, extrapolation of pharmacokinetic data to determine doses is a practical approach.

5 SAFETY REVIEW OF PEDIATRIC OTC COUGH AND COLD MEDICINES

5.1 Key Points

- Safety data findings from prospective clinical trials support that recommended doses of over-the-counter (OTC) cough and cold medicines are well tolerated in children.
- Given the extensive use of pediatric OTC cough and cold products, reports with major effects and fatal outcomes are rare. The limited number of fatalities that have been reported are mostly in children under 2 years of age, resulting from caregivers administering supratherapeutic doses of these medicine or secondary to accidental overdoses following ingestion of these products by curious young children who gain accidental and unsupervised access.
- In children <6 years of age, inadequate poison prevention in the home (inadequate measures to keep medicines out of the reach of children) leads to a significant number of accidental exposures. Despite this, overdoses resulting in toxicity and requiring healthcare evaluation and treatment are rare.
- Collectively, data from various sources suggest that medication/therapeutic errors with OTC cough and cold products in children may lead to unintentional overdose when:
    - Products are administered without using an appropriate measuring device
    - Confusion occurs between different product forms and varying concentrations
    - Multiple products containing the same or similar active ingredients are administered at the same time
    - Adult products are administered to children
    - Product labels do not provide dosing information and there is miscommunication between caregivers and healthcare providers, especially in children under 2 years of age
    - OTC cough and cold products are given for unlabeled uses (e.g. sedation) that may contribute to overdose.

In its Citizen Petition of March and May, 2007 (Docket 2007P-0074), The Baltimore City Health Department (BHD) cites evidence from the American Association of Poison Control Centers (AAPCC) and from the Maryland Poison Center (MPC). CHPA and its member companies requested and received additional information from both the American Association of Poison Control Centers (AAPCC) and the Maryland Poison Center (MPC), which is provided.

The BHD Petition also notes reports of fatality from the published literature, as well as four unpublished reports from the Maryland Office of the Medical Examiner. In this regard, CHPA has commissioned the Rocky Mountain Poison and Drug Center (RMPDC) to convene an independent expert medical panel whose objective is to review all available fatality cases in children under the age of 12 years associated with the use of OTC cough and cold products. The expert panel has obtained fatality cases from manufacturers' post-marketing adverse event reports (MedWatch Forms), the American Association of Poison Control Centers (AAPCC), the published English medical literature (including literature cited in the Baltimore Petition) and the Maryland Office of the Medical Examiner. At the time of this submission, the expert panel's review is still in progress.

CHPA and its member companies are also continuing the other activities to collect and analyze safety data in that a formal request has been submitted by CHPA to FDA for MedWatch reports with fatal outcomes from FDA's AERS and SRS databases; at the time of this submission, these reports have not yet been received. This section also provides a review of safety data from prospective clinical trials in children (published and unpublished).

5.2 Maryland Poison Center (2004)

The BHD Petition makes general reference to reports from the Maryland Poison Center (MPC) during the year 2004 involving OTC cough and cold medication in children. Additional details were requested from the Maryland Poison Center and a summary of the information received from MPC is provided in this section.

During 2004, the MPC reported 18,575 calls for all substances involving children < 6 years of age; 1078 (5.8%) of these involved cough and cold products [Maryland Poison Center 2007]. Using the standard AAPCC reasons for exposure (Appendix 4, Table 5.1), almost all (99.2%) of the calls (1069 of 1078) about a cough and cold product involving children < 6 years of age were not related to a therapeutic dose; such exposures were classified as unintentional general [n=757 exposures] or therapeutic error [n=312 exposures].[1] The remaining eight calls (<1%) were classified as an adverse reaction occurring with normal, prescribed, labeled or recommended use.

Using the standard AAPCC coding for medical outcomes (Appendix 4, Table 5.2), 1062 of 1078 exposures (98.5%) did not result in outcomes considered to be of significant severity

[1] According to standard Poison Center coding conventions, exposures by curious young children who gain accidental and unsupervised access to medicines are coded as unintentional general and cases of unintentional deviation from a proper therapeutic regimen (wrong dose, wrong route of administration, wrong person, wrong substance) are coded therapeutic error.

(Appendix 4, Table 5.3). In the 16 remaining cases, 11 were unable to be followed but were judged as a potentially toxic exposure and five other that were followed developed symptoms consistent with an outcome of a moderate effect. No major effects or deaths were reported. For the five cases developing a moderate effect, available case information suggests several possible reasons for overdose of a cough and cold medicine (Table 5.4). Four of the cases involved accidental ingestions of adult medicines by curious young children. The fifth case did not involve an oral medication, but was the result of administration of nose drops to an infant. All five children had complete resolution of symptoms.

Table 5.4 Maryland PC Cases (n=5) With a Moderate Effect Involving Cough and Cold Product In Children <6 Years of Age (2004)

Available Case Descriptions	Possible Reasons for Overdose
1-year-old was unintentionally exposed at home to an adult product containing acetaminophen and diphenhydramine. Within 10 minutes of the exposure the child was referred to the emergency department (ED). In the ED tremor, muscle twitching and a heart rate (HR) = 190 beats/min were noted. Treatment consisted of activated charcoal and oral N-acetylcysteine (NAC). Symptoms resolved within six hours. The child was discharged after completion of a three-day course of NAC therapy.	Inadequate poison prevention at home Ingestion of an adult medicine by a child
23-month-old was unintentionally exposed at home to an adult prescription cough syrup that contained chlorpheniramine and hydrocodone as well as an unidentified decongestant. The PC was contacted when the child became sleepy and had "jerky" movements. In the ED the child had a HR =137 beats/min, a blood pressure (BP) = 148/82 mmHg and a respiratory rate = 30 breath/min. Following 2 hrs of observation, the child had normal HR and BP, was awake and alert, and was discharged.	Inadequate poison prevention at home Ingestion of an adult medicine by a child
13-month-old was unintentionally exposed to an unknown number of diphenhydramine tablets. Several hours after the ingestion, the child became twitchy and agitated and was taken to the ED. In the ED the child was agitated, irritable and appeared to grab at things that weren't there. No treatments were administered and after several hours of observation the child was discharged although still slightly agitated. The agitation improved overnight and the child was well the next day.	Inadequate poison prevention at home Ingestion of an adult medicine by a child
3-year-old ingested approximately 2.5 ounces of an OTC syrup containing pseudoephedrine hydrochloride 15 mg/5 mL along with an unidentified antihistamine at home. In the ED a BP = 137/87 mmHg was noted but the child was otherwise well. Activated charcoal was administered. Within six hours of presentation to the ED the child was asymptomatic and discharged.	Inadequate poison prevention at home Ingestion of overdose amount
4-month-old was administered a dose of phenylephrine hydrochloride 0.125% nose drops by his mother to treat congestion. Soon after receiving the medication, the child reportedly became tremulous, developed grunting/difficulty breathing, and the feet and legs became "a little blue". Upon arrival in the ED there was no evidence of tremor or cyanosis. The HR was 170-190 beats/min with a systolic BP = 166 mmHg. An EKG was demonstrated tachycardia. The child was observed and discharged within eight hours.	Dosing information of OTC product in child < 2 years of age is not provided for on OTC label.

5.3 American Association of Poison Control Centers (AAPCC)

At the request of CHPA, AAPCC searched the National Poisoning Data System [NPDS, which was formerly Toxic Exposure Surveillance System (TESS)] for the time period of January 1, 2000 through June 30, 2007 for all applicable contacts, exposures and cases in children less than 12 years of age for products containing at least one or more prescription or OTC cough and cold ingredient (Appendix 5, Table 5.5). This section provides findings for the most frequently used OTC cough and cold ingredients, including brompheniramine, chlorpheniramine, diphenhydramine, dextromethorphan, doxylamine, guaifenesin, phenylephrine, and pseudoephedrine.

AAPCC is a not-for-profit nongovernmental association representing the United States' poison centers (PCs) serving all 50 states. Poison centers use a standard data collection form and follow established national procedures and definitions for data collection. An exposure does not necessarily represent a poisoning, overdose, or adverse reaction. Since some exposures may go unreported to PCs the data referenced from NPDS does not represent the true incidence of national exposures to any substance(s). The objectives of analyzing the AAPPC data from NPDS are to identify characteristics of the exposures to prescription and OTC cough and cold medications in children, to obtain case level data for fatal cases for review by an independent medical expert panel and to gain information to identify root causes.

Over the 6.5 year time period of this search of the NPDS, a total of 774,960 poison center contacts, exposures or cases were recorded for prescription and OTC cough and cold medications in children <12 years of age; 99% of these exposures occurred at home or at another residence. The most frequently recorded cough and cold ingredient categories were decongestants (48%), antihistamines (42%), antitussive (32%) and expectorant (9%).

Using AAPCC standard coding conventions (Appendix 4, Table 5.2), 97.3% of cases did not result in outcomes considered to be of significant severity as follows: not followed, minimal clinical effects possible (44.1%), no effect (29.3%), not followed, judged as a nontoxic situation (11.9%), minor effect (10.6%), unrelated effect (1%), or confirmed nonexposure (0.37%). The remaining cases (<3%) were coded as follows: unable to follow, judged as potentially toxic (1.7%), moderate effect (0.86%), major effect (0.04%), or death (0.0045%).

The majority (62%) of AAPCC cases were reported in children 2 to < 6 years of age, followed by 28% of exposures in children < 2 years of age. This age distribution is not unexpected since accidental exposures and overdoses by curious young children (2 to < 6

years of age) who gain accidental and unsupervised access are particularly common for virtually all OTC and prescription medicines within the AAPCC database [Lai 2006]. A small proportion of cases (11%) involved cases in children 6 to <12 years of age.

AAPCC uses standard coding conventions to record reasons contributing to the occurrence of medication exposures. In this dataset, it is estimated that approximately 35% of contacts, exposures or cases had a reason coded. Table 5.6 provides a summary of some of the AAPCC coded reasons contributing to exposures of cough and cold medicines in various pediatric age groups. The frequency of reasons is cumulative across a specific reason category (e.g. product stored inappropriately), but not within a specific age group.

Table 5.6 AAPCC Reasons For Exposures to Cough and Cold Medications In Children <12 years (y) of Age (2000-2007)

Reasons for Medication Exposure	0 to <2 y N (%)	2 to <6 y N (%)	6 to <12 y N (%)
Inadequate Measures To Keep Medicines Out of the Reach of Children			
Product stored inappropriately[a]	1422 (28.43%)	3465 (69.29%)	114 (2.28%)
Accessed medication in purse or suitcase	628 (27.78%)	1594 (70.50%)	39 (1.72%)
Product temporarily open	1586 (29.31%)	3677 (67.95%)	148 (2.74%)
Therapeutic/Medication Errors			
Other incorrect dose	14447 (31.24%)	22736 (49.16%)	9065 (19.6%)
Confused units of measure	4922 (32.03%)	7486 (48.72%)	2957 (19.25%)
More than one product containing same ingredient	2943 (23.52%)	6057 (48.41%)	3513 (28.07%)
Health professional iatrogenic	610 (64.08%)	249 (26.16%)	93 (9.77%)
Ten-fold Dosing Error	633 (70.81%)	195 (21.81%)	66 (7.38%)
Dispensing Cup Error	3867 (30.39%)	6337 (49.8%)	2522 (19.82%)
Incorrect Form Concentration Given and Dispensed	6325 (34.20%)	8549 (46.22%)	3621 (19.58%)

a. The frequency of reasons is cumulative across a specific reason category (e.g. product stored inappropriately), but not within a specific age group (e.g. 0 to <2 years of age).

AAPCC data shows that ten-fold dosing errors and health professional iatrogenic errors were more common in the children under 2 years of age compared to such errors in the other age groups. These findings may be related to the lack of dosing information for children under 2 years of age on the OTC label of cough and cold products, whereas, reasons related to inadequate poison prevention were more common in children 2 to <6 years of age compared to the other age groups. These findings highlight that medication exposures and overdoses appear to occur in situations in which cough and cold products are not kept out of the reach of young children, are stored inappropriately in the home, are left as open containers and children gain unsupervised access to purses and suitcases.

Over the 6.5 year time period of these AAPCC data, a total of thirty-five exposures to a cough and cold medication in children were reported with a fatal outcome. Table 5.7 provides a summary of AAPCC coded reasons contributing to fatal exposures involving cough and cold medicines in various pediatric age groups.

Table 5.7 AAPCC Reasons For Fatal Exposures to Cough and Cold Medications In Children <12 years (y) of Age (2000-2007)

Reasons for Medication Exposure	0 to <2 y (N=20)	2 to <6 y (N=12)	6 to <12 y (N=3)	0 to < 12 y (Total N=35)
Adverse Reaction	2	0	2	4 (12%)
Intentional Misuse	1	0	0	1 (2%)
Malicious	5	1	0	6 (17%)
Therapeutic Error	3	4	0	7 (20%)
Unintentional General	4	6	0	10 (29%)
Unknown reason	5	1	1	7 (20%)

Among the several reasons for fatal overdose in children under 2 years of age is an important finding of malicious intent (i.e. AAPCC definition: patients who are a victim of another person intent to harm them); this is almost exclusively found in children under 2 years of age compared to the other age groups.

The distribution of the fatal outcome cases by age suggest that children under 2 years of age, and especially under age one year, may be at risk for inadvertent overdose. Detailed information about the actual root causes is often missing for cases where parents truly made unintentional errors while trying to use products for intended therapeutic uses. It is unclear whether infants are more or less likely to have serious morbidity from a specific overdose, but that there are more cases of fatal overdoses in this age range is clear.

Overall, AAPCC findings of reasons leading to exposures of cough and cold medicines in young children (< 2 years of age) are consistent with findings from two published reports by the Centers for Disease Controls (CDC). The CDC analyzed 2001 – 2003 data for nonfatal, unintentional medication exposures in children ≤ 4 years of age to prescription and OTC medications from hospital emergency department (ED) visits [CDC 2006]. OTC medicines were involved in 42.2 % of all exposures. An estimated 72% of all exposures were in children aged 1-2 years and majority of the cases occurred in homes. Across all children, the most common sources of medication exposures were pills left out or pill bottles left open. Other incidents involved medications administered in error by parents or caregivers and children opening pill boxes or purses.

In its second report, the CDC and the National Association of Medical Examiners (NAME) described three infants aged < 6 months found dead in their home during 2005 in which prescription and OTC cough and cold medications were determined by medical examiners or coroners to be the underlying cause [CDC 2007}. On autopsy, two cases had evidence of respiratory failure; no abnormalities of cardiac pathology were revealed in any of the infants. The post-mortem pseudoephedrine blood levels (4,743, 6,832 and 7,100 ng/mL) in these infants were approximately 9 to 14 times the levels expected from administration of recommended doses to children 2 to12 years of age. Table 5.8 provides the reported case information.

Table 5.8 CDC and NAME Survey - Case Descriptions [CDC 2007]

Available Case Descriptions	Possible Reasons for Overdose
A one-month male received a prescription medication containing pseudoephedrine (PSE), dextromethorphan and carbinoxamine; underlying cause of death was pseudoephedrine intoxication; significant medical conditions or contributing factors included interstitial pneumonia and recent hospitalization for fever.	Ingestion of an adult prescription medicine by an infant
A six month old female received a prescription medication containing pseudoephedrine, dextromethorphan and carbinoxamine plus an OTC medication containing pseudoephedrine and acetaminophen; underlying cause of death was pseudoephedrine and dextromethorphan intoxication; autopsy showed bronchopneumonia and empyema.	Administration of two medicines containing the same active ingredient at the same time
A three month old male received an OTC medication containing pseudoephedrine and acetaminophen; post-mortem blood levels also found doxylamine and dextromethorphan; significant medical conditions or contributing factors included the infant was found lying in crib in a prone position, a reported history of colic, born preterm (33 weeks) and a small fracture of left distal tibia; acute anoxic encephalopathy on autopsy.	Suspicious circumstances

5.4 Safety Data From Prospective Clinical Trials in Children

This section provides a summary of safety findings from prospective clinical trials and post-marketing safety studies in children <12 years of age for single ingredient and combination OTC cough and cold products. Appendix 5, Table 5.9 provides a detailed listing of each study including design, methods, sample sizes, treatments, subjects and safety findings. Overall, the reported adverse events were of mild to moderate severity. The adverse events recorded were as expected based upon the mechanism and pharmacology for each ingredient. There was a single pseudoephedrine exposure in a 22-month female from a post marketing surveillance study that reported a seizure whose causality was considered remote.

The OTC cough and cold ingredients varied in terms of number of clinical studies conducted and subjects exposed. In prospective clinical studies, pseudoephedrine had the largest number of exposures (n=1141 subjects), which was followed by chlorpheniramine (n=450 subjects), dextromethorphan (n=231 subjects) and brompheniramine (n=230 subjects). The other OTC cough and cold ingredients had a

limited number of subject exposures. There is limited safety data from these clinical trials in pediatric age subsets of <2 years. In conclusion, safety data findings from prospective clinical trials support that recommended doses of over-the-counter (OTC) cough and cold medicines are well tolerated in children.

5.5 Summary

- Safety data findings from prospective clinical trials support that recommended doses of over-the-counter (OTC) cough and cold medicines are well tolerated in children.
- Given the extensive use of pediatric OTC cough and cold products, reports with major effects and fatal outcomes are rare. The limited number of fatalities that have been reported, are mostly in children <2 years of age, resulting from caregivers administering supratherapeutic doses of these medicine or secondary to accidental overdoses following ingestion of these products by curious young children who gain accidental and unsupervised access.
- In children <6 years of age, inadequate poison prevention in the home (inadequate measures to keep medicines out of the reach of children) leads to a significant number of accidental exposures. Despite this, overdoses resulting in toxicity and requiring healthcare evaluation and treatment are rare.
- Collectively, data from various sources suggest that medications errors with OTC cough and cold products in children may lead to unintentional overdose when:
    - Products are administered without using an appropriate measuring device
    - Confusion occurs between different product forms and varying concentrations
    - Multiple products containing the same or similar active ingredients are administered at the same time
    - Adult products are administered to children.
    - Healthcare providers provide inaccurate instructions or caregivers misunderstand their instructions, especially in children < 2 years of age.
    - OTC cough and cold products are given for unlabeled uses (e.g. sedation) that may contribute to overdose.
- CHPA and its member companies are continuing a number of activities to collect and analyze safety data.

6 INSIGHTS ON PARENTS, CAREGIVERS, AND HEALTHCARE PROFESSIONALS

6.1 Key Findings

- The experience of parents and caregivers, especially when they have multiple children, plays a key role in determining whether they ask a healthcare professional for advice about administering an OTC cough and cold medicine to their children.
- Parents and caregivers have very little understanding about active ingredients and rarely ever look at that section of the label.
- Parents and caregivers do not report difficulty successfully using dosing devices when administering OTC cough and cold medicines to their children.
- Healthcare professionals are reluctant to recommend OTC cough and cold medicines to children under 2 years of age.
- Healthcare professionals are more likely to recommend OTC cough and cold medicines to children 2 years of age and older.
- Parents and caregivers likely would not administer any medication to their children if it were labeled “do not use.”

6.2 Parents and Other Caregivers

CHPA commissioned a qualitative survey during the summer of 2007 to gain a better understanding of how parents and other caregivers perceive OTC cough and cold medicines for their children, how they administer these medications to children, the type of communication they have with pediatricians and other healthcare professionals regarding use, and if there are gaps to general safe use [West Mill Marketing 2007]. The survey consisted of 66 in-depth caregiver interviews. All interviewees were caregivers of children 6 years of age or younger and had previously administered OTC cough and cold medicines to the child(ren) in their charge. Sixteen respondents cared for children under 6 months of age, 29 respondents cared for children 6 months to 2 years of age, and 28 respondents cared for children 2 years to 6 years of age. Some respondents had more than one child within the age ranges. The interviews were conducted in Edison, New Jersey, and Kansas City, Missouri. Respondents included 46 mothers, 11 fathers, and nine caregivers (other than mothers or fathers). The respondents were from a mix of ethnic backgrounds: 30 were Caucasian, 13 African-American, 16 Hispanic, and 7 Asian. Education and household income varied.

Below is a summary and analysis of these findings. CHPA additionally is conducting a quantitative study (fielded September 13, 2007) which will be presented at the FDA advisory committee meeting on October 18, 2007.

6.3 Overview of Findings from Parents and Other Caregivers

The overwhelming reason cited by respondents for giving OTC cough and cold medications to their children was to help their children feel better. Almost all study respondents described themselves as generally comfortable administering these medicines to their children under 6 years old. While education level, income level, or ethnic background did not have an impact on a respondent's adherence to the recommended administration of OTC cough and cold medicines or attitude toward asking a healthcare professional for assistance, two influencing factors did emerge:

1. Perception of OTC medicines as either "serious" medications or as "safe" medications, and
2. Experience of the caregiver generally related to the number of children in the household. Those with more than one child in the household stated that they did not need to talk to a doctor when they could rely on their memory from previous experiences to determine a child's dose.

A majority of respondents admitted to reading only portions of the Drug Facts label.

- Almost all reported reviewing the front of a medicine package (for the product name or brand family, the symptoms the medicine treats, and package graphics that would tend to indicate if the medicine is appropriate for young children).
- Almost all reviewed the dosing directions. Respondents overwhelmingly said the dosing directions were clear and easy to find.
- A smaller number also reviewed the warnings section.
- All respondents recalled seeing "ask a doctor" on medications, but most did not have an understanding of why "ask a doctor" would be on a label rather than specific dosing instructions.
- **Almost all respondents indicated that they would not administer any medication to their child if it were labeled "do not use."**

This qualitative study also highlighted consumers' lack of understanding about active ingredients. A medication's active ingredient(s) played a negligible part in the selection

process; rather, respondents based their selection decisions on the child's symptoms; brand names; and recommendations of pediatricians, family, and friends.

This lack of understanding about active ingredients was underscored when respondents were questioned about the concomitant administration of multiple medications.

- Most were reluctant to dose their children with two different medications at the same time. However, a small minority, viewing OTCs as "safe," expressed very little concern about dosing with multiple medications.
- Almost all said they would first ask their doctor or pharmacist for advice before administering multiple medications to their children. Many voiced concerns over the potential for overdose when dosing with two medications containing the same active ingredient. Others guessed that the two medicines with the same active ingredient would be compatible.

This study did not uncover any physical obstacles to the actual administration of OTC cough and cold medicine to children. Most caregivers reported using the dosing device provided with a medication and were fully confident in their abilities to accurately administer the correct amount of a particular medication.

- Almost all respondents reported having other dosing devices on hand in case none were supplied with the particular OTC medication.
- The majority of study respondents did not express difficulty maintaining a dosing schedule for their child, even when multiple caregivers are involved.

This qualitative study found the following results when caregivers were asked how much medicine to give a child, or how frequently to administer the medication:

- **59% of respondents indicated they would ask a healthcare professional for help.** These caregivers typically expressed an appreciation of getting the dose correct and reported having access to 24-hour healthcare services, such as a doctor's office, nurse helpline, or pharmacy.
- **27% indicated they would be more likely to make their own decisions** without contacting a healthcare professional. This group was hesitant to bother their doctor, didn't want to wait for a return phone call from a healthcare professional, or felt that OTC medicines are safe enough that they didn't need to be concerned with exact dosing recommendations. This group also relied heavily on advice from friends or relatives, and, in some cases, used dosing instructions for one medication as the correct dose for a different medication.

- **14% of respondents indicated that they would likely contact a healthcare professional only during regular business hours**, expressing reticence towards interrupting a busy pharmacist or trying to contact a healthcare professional outside of business hours or if they were in a hurry to get a response.

When caregivers did not consult a healthcare professional, the following methods were most frequently cited as techniques used by this group to determine dosage:

- Using half of the lowest recommended dose on the label
- Using the lowest dose marked on the dosing device included with the medicine
- Using the same dose their doctor or pharmacist recommended to them for another medicine

When questioned about alternative therapies, the study found the following:

- Many study respondents used a humidifier to help treat a cold, and were generally satisfied with this method.
- A slight majority of the many respondents who reported having tried chest rubs were satisfied, citing messiness as a reason for dissatisfaction.
- Less than half of the respondents used a saline nose spray for mucus removal; most of these respondents, however, were satisfied, but some indicated that sprays were difficult to use with young children.
- Most study respondents had not tried either menthol or eucalyptus room fresheners or herbal bathing salts for treating a cough or cold symptoms.

6.4 Healthcare Professionals

CHPA and its member companies have used a number of research tools to better understand the perceptions and uses of OTC cough and cold medicines among pediatricians and other healthcare providers. In particular, these findings show a high level of comfort among pediatricians with these products in children ages 2 years and above. There is less of a comfort level and somewhat of a reluctance to recommend these medicines for children under 2 years of age and especially for children under 9 months of age [West Mill Marketing 2007]. Research also shows that pediatricians stand out as the key sources of information and advice about medications for children under the age of 2 years [Proprietary data from Weinman Schnee Morais Inc. 2007].

6.5 Overview of Findings from Healthcare Professionals

Healthcare professionals, including physicians and pharmacists in this report, cite a high-degree of communication with parents, especially new parents, regarding OTC cough and cold medicines for children.

- The majority exercise caution regarding whether to recommend an OTC cough and cold medication for a child, most reporting caution or reluctance to recommend these medications for children under the age of 2 years. The majority do recommend OTC cough and cold medicines for children over the age of 2 years.
- Almost all physicians cited a paucity of guidelines for recommending the use of OTC cough and cold medicines for their young patients.
- Healthcare professionals also reported a lack of awareness of active ingredients in OTC cough and cold medicines among parents.
- Healthcare providers see the key benefits of cough and cold medications as symptom relief followed by a good night's sleep [Proprietary data from Market Tools/Healthcare 2007].

Three hundred healthcare professionals surveyed expressed the following attitudes about recommended courses of treatment for children with a cough and/or cold:

- Most say they are generally cautious with children under the age of 2 years of age, and some say they are more cautious with children under the age of 12 months.

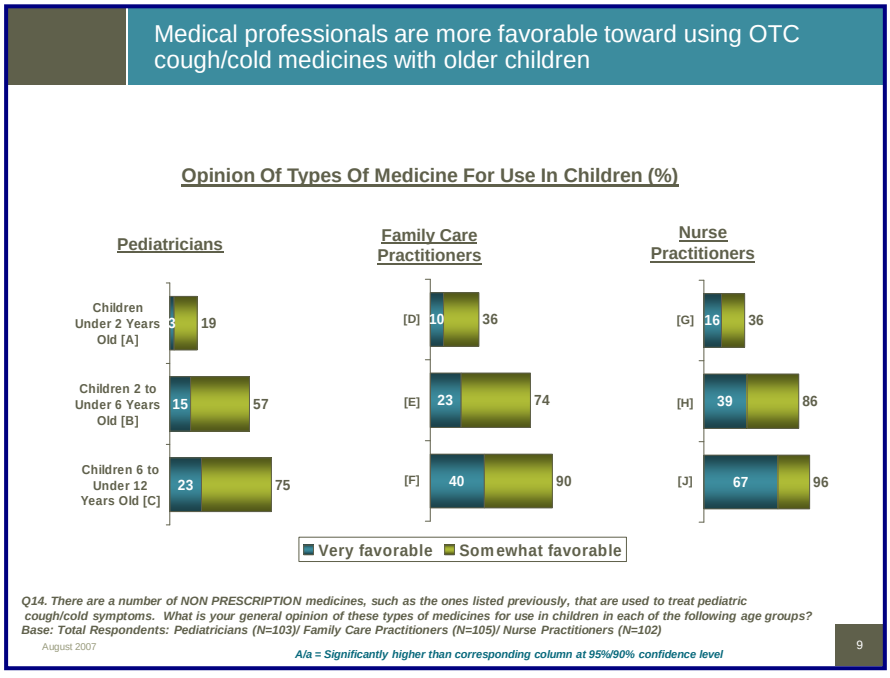
- The majority of respondents say that they are more comfortable and less cautious recommending OTC cough and cold medicines to children once they are past the age of 2 years.

Healthcare professionals recognize that experience is an important determinant of whether caregivers seek out their advice when it comes to OTC cough and cold medicines.

- Most study respondents indicate that new parents are the most cautious and ask for help with the use of an OTC cough or cold medicine.
- Experienced parents (those with more than one child) rely more on their own experience to make decisions.
- Most physician respondents feel that they have the most influence with the use of an OTC cough and cold medicine with their patients who are under 6 months of age.
- The majority of physician and pharmacist respondents say that they do not have a great concern about the difficulty patients or customers might have using the dosing devices that come with OTC cough and cold medicines.

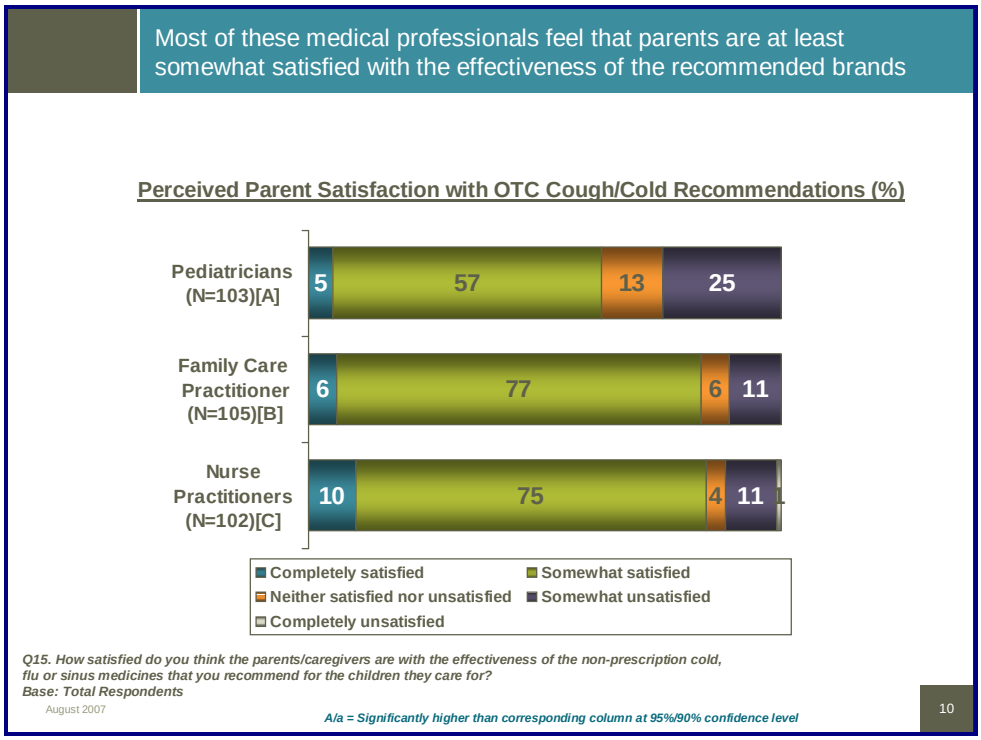
Almost all physicians say that they have no real guidelines for recommending the use of OTC cough or cold medicines for their young patients. They rely on their experience. When required to recommend dosing, respondents mentioned several methods:

- Cutting the dose that is included on the package label (usually by ½ of the label dose, or sometimes by ¼ of the label dose for younger or smaller (weight) children)



[Proprietary data from Market Tools/Healthcare 2007]

- Referencing product ingredients in the *Pediatric Dosing Handbook* or the *Facts and Comparison* reference book to calculate dosing
- Some pharmacists say they rely on memory of what doses pediatricians have recommended in the past.



[Proprietary data from Market Tools/Healthcare 2007]

6.6 Conclusions

Qualitative research conducted with parents, other caregivers, and healthcare professionals, underscores the lack of understanding about active ingredients by parents and other caregivers. While generally familiar with the front of OTC cough and cold medicine packages and with the Drug Facts label, this important segment of consumers reads only portions of the label, namely, the symptoms the medicine treats, the dosing directions, and, sometimes, the warnings. Parents and other caregivers rely on the advice of physicians, pharmacists, relatives, and friends when they have questions about OTC cough and cold medicine dosing for their children. Parents and other caregivers, however, do not report any particular questions or difficulties with dosing devices or dosing schedules.

Investigation into the habits of parents and other caregivers, and into the perceptions of healthcare professionals, point to a number of conclusions:

- Parents and other caregivers are motivated by a sincere desire to make their children feel better when suffering from cough and cold symptoms, and are therefore ripe for educational efforts.

- Parents and other caregivers need additional educational efforts to explain the importance of paying attention to active ingredients.

- Parents and other caregivers rely upon healthcare professionals for advice regarding OTC cough and cold medications for children. Healthcare professionals must be integrated into any systematic, industry-wide effort that involves the changing of OTC cough and cold medications' labels for children under the age of 2 years.

7 RECOMMENDED ACTION PLAN

7.1 Key Points

CHPA and its member companies recommend the following steps to promote appropriate use of OTC cough and cold medicines in children:

- A risk minimization plan to help reduce overdose and misuse of OTC cough and cold medicines, which includes proposed label recommendations, educational initiatives, and observational studies. The proposed label recommendations include:
    - Changing “Ask a doctor” to “Do Not Use” in children under 2 years of age
    - Adding “Do not use to sedate children” or similar language for monograph antihistamines
- A pediatric research program of pharmacokinetic studies in children 2 to under 12 years of age to confirm or refine recommended doses.

7.2 *Risk Minimization Plan*

While the available data supports that recommended doses of OTC cough and cold medicines are well tolerated in children, rare adverse events, including death, have been reportedly associated with the overdose and misuse of these medicines, especially in young children. To address overdose and misuse of these medicines, a comprehensive risk minimization plan is proposed. This plan includes the following components:

- Specific label changes that pertain to young populations, including:
    - “Do not use” in children under 2 years of age
    - Language on monograph antihistamines to indicate “Do not use to sedate children”
- A multi-year, national education campaign to reinforce the importance of following OTC label directions and to enhance ongoing efforts to reduce overdose and misuse in children
- Prospective safety study to reaffirm the safety of OTC cough and cold medicines at recommended doses

7.2.1 Overview

The root causes of deaths and serious adverse events reportedly associated with the use of OTC cough and cold medicines in children are still under review, but several high risk scenarios and behaviors are apparent:

- Overdose and misuse in children less than 2 years of age
- Unintentional accidental exposure by curious young children (inadequate measures to keep medicines out of reach of children)
- Use of medicines for unlabeled indications, especially sedation
- Use of medicines intended for adults in children
- Use of multiple medicines containing the same or similar ingredients at the same time

When used inappropriately, OTC cough and cold products can pose risks, especially to young children under 2 years of age. Label changes along with strong educational programs directed at both consumers and healthcare professionals can help reduce this risk. CHPA is committed to addressing the main concerns discussed above. We have outlined the following goals that seek to reduce overdose due to misuse and unintentional accidental exposure:

7.2.2 Goals

1. Caregivers use OTC cough and cold medicines only for labeled indications and only in recommended doses.
2. OTC cough and cold medicines are only used in the age range for which they are indicated.
3. Adult products are not used in children.
4. Caregivers do not use OTC cough and cold medicines in children younger than 2 years of age.
5. OTC monograph antihistamines are not used to sedate children.
6. Caregivers do not use multiple medications with the same or similar active ingredients in children at the same time.
7. Medicines are kept out of the reach of children.

CHPA and its members will address these goals through proposed label changes and an aggressive national education campaign.

7.2.3 Proposed Label Recommendations

CHPA and its members recommend enacting strong label changes on OTC cough and cold medicines to help reduce overdose and misuse. Our highest priority is continuing to provide caregivers with all the information necessary to use these medicines appropriately.

CHPA and its members recommend that dosing directions on OTC cough and cold medicines for children 0 to under 2 years of age be changed from “ask a doctor” or “consult a physician” to read “Do Not Use.” The spirit of “ask a doctor” was to encourage parents and other caregivers to discuss symptoms, as well as dosing recommendations, with a healthcare provider. Cases of overdose and misuse associated with pediatric OTC cough and cold medicines have been reported. This label change is intended to help prevent consumer misuse and overdose. This label change should not be misunderstood to suggest that the appropriate use of these medicines at the specific direction of a healthcare provider is unsafe.

The following factors support these recommendations: the challenge of obtaining pharmacokinetic data in this age group; a proportionately higher number of fatal outcomes from overdose in children under 2 years of age; and the absence of dosing information in the OTC monograph and on the label.

Additionally, adverse events have been reported related to caregivers administering monograph antihistamines for sedation of children. As this is not an indication for use of these ingredients in children, CHPA and its members strongly recommend adopting language on the label warning caregivers not to use these medicatines for sedation.

These label changes are important to communicate these key messages to parents, caregivers, and healthcare providers. In addition, these messages should be reinforced with a national education campaign targeting both consumer and healthcare professionals.

7.2.4 Education

CHPA is developing an industry-wide, multi-million dollar, multi-year national initiative to educate parents and other caregivers on the appropriate use of OTC medicines in children. The campaign will be conducted by CHPA’s nonprofit, educational foundation, the Consumer Health Education Center (CHEC).

This campaign will be inclusive in its efforts by enlisting the expertise of various national medical and consumer organizations and governmental agencies. The goals of the initiative will be:

- To educate consumers, particularly parents, about appropriate use of cough and cold medicines in children.
- To educate healthcare professionals about recommended label changes and to encourage healthcare professional/parental communication.
- To encourage parents to discuss children's symptoms with their healthcare providers

Of primary importance in the development of the CHEC campaign is the establishment of key partnerships with a broad range of organizations with diverse outreach in order to verify messaging and maximize reach through distribution channels. The partners in the campaign will create educational materials in hardcopy, electronically, and utilizing new or multi-media. In addition, appropriate pediatric dosing messages will be presented directly at tactical points in consumers' lives, such as in hospital maternity wards, pediatricians' offices, and at the point-of-purchase. The distribution of messages will be multiplied with a strategic use of media through earned media (news releases, press conference, notable spokesperson, media tours, etc.), paid advertising, and public service announcements. Moreover, CHEC will create mutual relationships with online health information providers to ensure visibility of the importance of appropriate pediatric dosing and the scientifically valid messages of the campaign.

7.2.5 Measurements

An important aspect of the risk minimization plan is the measurement of the impact of goals and objectives outlined above. To do this, CHPA will establish clearly defined tools and goals to measure the impact of these initiatives, including measuring both the attitudes and behaviors of caregivers and healthcare professionals prior to and throughout the lifecycle of this campaign, in addition to standard public relations metrics.

Additionally, CHPA will continue to work with the American Association of Poison Control Centers and its members to develop systems to better understand the behaviors around misuse.

7.2.6 Observational Study

CHPA member companies recommend conducting an observational study to be initiated by industry in 2008. The primary objective of this prospective study is to further confirm the safety profile of cough and cold ingredients at recommended doses. FDA advice on the methodology and protocol will be sought prior to commencement of the study.

7.3 Proposed Pediatric Research Program

As discussed in Section 4 of this document, pediatric pharmacokinetic (PK) data confirm that current pediatric OTC doses for pseudoephedrine and chlorpheniramine align with those doses showing efficacy in adults. While PK data in adults are available for all ingredients discussed herein, additional pediatric PK data can further confirm or refine doses for other ingredients. Therefore, CHPA member companies recommend and have begun discussions with FDA about the conduct of pharmacokinetic studies in children 2 to under 12 years of age for the following ingredients:

- Dextromethorphan
- Phenylephrine
- Guaifenesin
- Brompheniramine
- Diphenhydramine
- Doxylamine

The main objectives for the pediatric PK studies are:

- To determine whether maximum and total systemic drug exposures for current pediatric doses are comparable to those for adult doses
- To assess whether the dose-concentration relationship is age-dependent after adjustment for differences in body size

CHPA and its member companies are working expeditiously to identify research facilities that have the expertise and capacity to undertake pharmacokinetic studies in children. Our targeted timeframe for completing these studies and sharing the results with the agency is 12 to 24 months after the initiation of the studies.

7.3.1 Evaluation of Other Determinants

In parallel to conducting pediatric PK studies, we are committed to working in close cooperation with FDA and other experts to identify strategies to bridge efficacy data, including the development of validated, pediatric pharmacodynamic or clinical symptom endpoints.

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Appendix 1: Pharmacokinetic and Efficacy Summaries for Eight OTC Cough-Cold Ingredients

A 1-1. **Pharmacokinetic and Efficacy Summaries for OTC Brompheniramine**

1. Active Ingredient
   - Name of ingredient: Brompheniramine maleate
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	2 mg every 4-6 hr, not to exceed 12 mg in 24 hr	4 mg every 4-6 hr, not to exceed 24 mg in 24 hr	"Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

Brompheniramine maleate

Publication Reference & Study Characteristics	***Simons et al. 1999;*** Single-dose study in 14 children (age 9.5 ± 0.4 yr, weight 31.9 ± 1.7 kg); **syrup**	***Simons et al. 1982a;*** Single-dose study in 7 adults (age 28 ± 11 yr, weight 72.8 ± 13.5 kg); **syrup**
Results:	**Children 4 mg dose**	**Adults 9.8±1.7 mg dose**
AUC *(ng/mL/hr)*	127 ± 18	293 ± 32
tmax *(hr)*	3.2 ± 0.3	3.1 ± 1.1
Cmax *(ng/mL)*	7.7 ± 0.7	11.6 ± 3.0
Vd *(L/kg)*	20.0 ± 1.8	11.7 ± 3.1
t½ *(hr)*	12.4 ± 1.1	24.9 ± 9.3
Cl *(mL/min/kg)*	20.2 ± 2.1	6.0 ± 2.3

5. Efficacy Study Summaries for Brompheniramine

These summaries are from published randomized, placebo-controlled studies of brompheniramine alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Hutton et al. 1991	[see below]			
	Clemons et al. 1997	[see below]			
6 months - <6 years	Hutton et al. 1991	Double-blind placebo (n=27)-controlled trial of fixed combination (n=36) of brompheniramine, phenylephrine, & phenylpropanolamine in children (0.5-5 yr, mean 25 ± 15.7 months) with signs of upper respiratory infection (i.e., nasal congestion or rhinorrhea); also a "no treatment" group (n=33)	Fixed combination of brompheniramine maleate (4 mg/5 ml), phenylephrine HCl (5 mg/5 ml), & phenyl-propanolamine HCl (5 mg/5 ml) given 3 times/ day so that brompheniramine dosage was 0.5-0.75 mg/kg body weight/day for 2 days	Parents' subjective assessment of symptoms (congested or runny nose, breathing trouble, fever, cough, decreased appetite, crankiness, sleep disturbance, & excessive sleepiness) at 48 hr	No differences among groups in individual or composite symptom score changes
	Clemons et al. 1997	Double-blind placebo (n=31)-controlled trial of a combination (n=28) of brom-pheniramine & phenylpropanolamine in children (0.5-5 yr) with upper respiratory infections (<7 days' duration)	Combination of brom-pheniramine maleate (2 mg/5 ml) & phenyl-propanolamine HCl (12.5 mg/ml): 0.5 tsp for children 6 mo-2 yr & 1 tsp for those 2-5 yr, no more often than every 4 hr & no more than 4 doses, for 48 hr	Parents' subjective assessment 2 hr after each dosage of change in symptoms (runny nose, nasal congestion, & cough) & whether child was sleeping	No statistically significant differences in symptom improvement between groups, but higher proportion of treated children sleeping 2 hr after dosage
6 - <12 years	No studies available				

≥12 years & Adults	Gwaltney & Druce 1997	Double-blind placebo (n=112)-controlled trial of bromphenir-amine (n=113) in subjects with induced (rhinovirus type 16) colds	Brompheniramine maleate 12 mg 2 times/day for ≤4 days	Daily nasal secretion weights, 12-hr sneeze & cough counts; subjective symptom (sneezing, rhinorrhea, nasal obstruction, sore throat, cough, headache, malaise, chilliness) scoring and global evaluations	Lower nasal secretion weights, lower sneezing counts & severity scores, lower cough counts, lower total symptom scores with brompheniramine, which was efficacious for treating sneezing, rhinorrhea, & cough

A 1-2. **Pharmacokinetic and Efficacy Summaries for OTC Chlorpheniramine**

1. Active Ingredient
   - Name of ingredient: Chlorpheniramine maleate
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	2 mg every 4-6 hr, not to exceed 12 mg in 24 hr, "or as directed by a doctor."	4 mg every 4-6 hr, not to exceed 24 mg in 24 hr, "or as directed by a doctor."	"Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

Chlorpheniramine maleate

Publication Reference & Study Characteristics	***Thompson et al. 1981;*** Single-dose study in 7 patients aged 6 – 14 yr (weight 24 - 36 kg); **intravenous solution**	***Simons et al. 1982b, Simons et al. 1984;*** Single-dose study in 11 patients aged 6 – 16 yr (mean age 10.95 ± 2.98 yr, weight 39.63 ± 9.19 kg); **syrup**	***Kotzan et al. 1982;*** Single-dose study in 15 healthy male volunteers aged 18 – 27 yr (mean age 21 yr, mean weight 74 kg); **syrup**	
Results:	**Children 0.1 mg/kg i.v. dose**	**Children 0.12 mg/kg** (corr. to mean dose of **4.8 mg** on basis of mean weight)	**Adults**	
			4 mg dose	**8 mg dose**
AUC *(ng/mL/hr)*	*not reported*	246 ± 125	65.4 ± 21.8	156.3 ± 60.7
t_{max} *(hr)*	*not reported*	2.5 ± 1.5	3.4 ± 2.5	3.8 ± 2.7
C_{max} *(ng/mL)*	*not reported*	13.5 ± 3.5	5.9 ± 2.3	11.3 ± 2.9
Vd *(L/kg)*	3.81 ± 1.46	7.0 ± 2.8	*not reported*	*not reported*
t½ *(hr)*	9.6 ± 3.6	13.1 ± 6.6	14.6 ± 3.4	17.3 ± 4.4
Cl *(mL/min/kg)*	5.38 ± 1.5	7.23 ± 3.16	*not reported*	*not reported*

5. Efficacy Study Summaries for Chlorpheniramine

These summaries are from published randomized, placebo-controlled studies of chlorpheniramine alone or in combination with other drug active ingredients and a meta-analysis of data from randomized, placebo-controlled studies.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Sakchainanont et al. 1990	[see below]			
1.5 months - <6 years	Sakchainanont et al. 1990	Double-blind placebo (n=47)-controlled trial of chlorpheniramine (n=48) and clemastine (n=48) in children 1.5-60 months old (mean 23±16.12) with rhinorrhea with or without occasional non-productive cough of 3 days' duration	Chlorpheniramine maleate 0.35/kg/day 3 times/day or clemastine fumarate 0.05 mg/kg/day 2 times/day for 3 days; medications and placebo each in equal volumes of 0.5ml/kg/dose	Subjective evaluation of symptoms (nasal discharge, nasal turbinate edema, cough)	Statistically significant improvement of every symptom in every group; no benefit of treatment shown except in children with copious nasal discharge; amount of nasal discharge reduced in 25/48 children with chlorpheniramine, 28/48 with clemastine, and 22/47 with placebo
6 - <12 years	No studies available				
≥12 years & Adults	Howard et al. 1979	Placebo (n=138)-controlled trial of chlorpheniramine (n=133) in subjects with signs & symptoms of common cold for 24-48 hr	Chlorpheniramine maleate 4 times/day (dose not specified) for 6 days	Subjective evaluation of symptoms by subjects (runny nose, stuffy nose, sneezing, postnasal drip, cough, watery eyes, & overall condition) & physicians (nasal swelling, redness, secretions, & obstruction & overall	Chlorpheniramine superior to placebo in lessening the degree of symptoms; statistically significant differences on 1st day & as late as the 7th day

				condition)	
	Crutcher & Kantner 1981	Double-blind placebo (n=54)-controlled trial of chlorpheniramine (n=52) in subjects (18-65 years old) with onset of a cold <48 hr	Chlorpheniramine maleate (marketed OTC product, presumably 4 mg) 4 times/ day for 7 days	Subjective evaluation of symptoms (runny stuffy nose, sneezing, postnasal drip, cough, & sore throat) by subjects & of signs (nasal swelling, redness, secretions, and nasal obstruction) by physicians	Chlorpheniramine significantly effective in relieving cold symptoms and showed a clear trend toward reducing signs of a cold
	Doyle et al. 1988	Double-blind placebo (n=18)-controlled trial of chlorpheniramine (n=19) in subjects (18-44 yr) with induced (rhinovirus type 39) colds	Chlorpheniramine (salt not specified) 4 mg every 4 hr (24 mg/day) for 5 days	Objective assessment of nasal patency (by rhinomanometry), eustachian tube function (by 9-step test & sonotubametry), middle ear pressure (by tympanometry), & nasal clearance (by dyed-saccharin technique); nasal secretions quantified; objective evaluations of symptoms (malaise, rhinorrhea, sneezing, and nasal congestion) by subjects	Chlorpheniramine effective in decreasing sneezing and nasal secretions and in increasing mucociliary clearance; no difference between groups in objective measures of nasal congestion or response of middle ear & eustachian tube
	Gaffey et al. 1987	Double-blind placebo (n=11)-controlled trial of chlorpheniramine (n=10) in subjects with induced (rhinovirus type 29) colds	Chlorpheniramine maleate 4 mg 4 times/day (16 mg) for 4 days	Expelled nasal mucus weight measured & used nasal tissues counted; clinical symptoms monitored to determine frequency & severity of clinical illness	Chlorpheniramine not shown to have a significant effect on nasal symptoms or nasal mucus production

	Gwaltney et al. 2002	Double-blind placebo (n=30) controlled trial of a combination (n=61) of chlorpheniramine & ibuprofen [against a combination (n=59) of intranasal interferon (IFN)-α2b + chlorpheniramine + ibuprofen] in subjects 18-51 years old) with induced (rhinovirus type 39) colds	Chlorpheniramine maleate 12-mg sustained-release tablet + ibuprofen 400 mg every 12 hr for 4.5 days (with or without concomitant intranasal administration of IFN-α2b 6 x 10^6 U 3 times)	Nasal mucus weight determined for 24-hr periods; symptom (sneezing, runny nose, nasal obstruction, sore throat, cough, headache, malaise, & chilliness) data collected daily	Reduction in severity of rhinorrhea, sneezing, nasal obstruction, sore throat, cough, & headache & in nasal mucus production, & nasal tissue use with treatment; enhanced effectiveness with concomitant administra-tion of IFN-α2b
	D'Agostino et al. 1998	Meta-analysis of raw data from 8 double-blind studies (placebo-controlled), including 3 on chlorpheniramine, to evaluate effective-ness of antihistamines to reduce symptoms of runny nose & sneezing over the first 2 days of medication for sub-jects having common colds for 24-48 hr	Chlorpheniramine at 4 mg 4 times/day	Statistical analysis of data on severity of runny nose & sneezing	Homogeneity of treatment effect across studies & consistency confirmed for pooling the studies; antihistamines shown to be statistically significantly more effective than placebo in reducing severity of runny nose and sneezing

A 1-3. **Pharmacokinetic and Efficacy Summaries for OTC Diphenhydramine**

1. Active Ingredient
   - Name of ingredient: Diphenhydramine citrate; diphenhydramine hydrochloride
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	*For products containing diphenhydramine citrate:* 19-38 mg every 4-6 hr, not to exceed 228 mg in 24 hr *For products containing diphenhydramine hydrochloride:* 12.5-25 mg every 4-6 hr, not to exceed 150 mg in 24 hr	*For products containing diphenhydramine citrate:* 38-76 mg every 4-6 hr, not to exceed 456 mg in 24 hr *For products containing diphenhydramine hydrochloride:* 25-50 mg every 4-6 hr, not to exceed 300 mg in 24 hr	*For products containing diphenhydramine citrate:* "Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours." *For products containing diphenhydramine hydro-chloride:* "Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

Diphenhydramine hydrochloride

Publication Reference & Study Characteristics	***Simons et al. 1990;*** Single-dose study in 21 subjects divided into 3 groups: **syrup** - children (age 8.9 ± 1.7 yr, weight 31.6 ± 6.8 kg) - young adults (age 31.5 ± 10.4 yr, weight 70.3 ± 9.9 kg) - elderly adults (age 69.4 ± 4.3 yr, weight 71.0 ± 11.4 kg)		
Results:	**Children 39.5±8.4 mg dose**	**Young Adults 87.9±12.4 mg dose**	**Elderly Adults 86.0±7.3 mg dose**
AUC *(ng/mL/hr)*	475 ± 137	1031 ± 437	1902 ± 572
tmax *(hr)*	1.3 ± 0.5	1.7 ± 1.0	1.7 ± 0.8
Cmax *(ng/mL)*	81.8 ± 30.2	133.2 ± 37.6	188.4 ± 54.5
Vd *(L/kg)*	17.9 ± 5.9	14.6 ± 4.0	10.2 ± 3.0
t½ *(hr)*	5.4 ± 1.8	9.2 ± 2.5	13.5 ± 4.2
Cl *(mL/min/kg)*	49.2 ± 22.8	23.3 ± 9.4	11.7 ± 3.1

5. Efficacy Study Summaries for Diphenhydramine

These summaries are from published randomized, placebo-controlled studies of diphenhydramine alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	No studies available				
2 - <6 years	Paul et al. 2004	[see below]			
2 – 16.5 years	Paul et al. 2004; Yoder et al. 2006	Double-blind placebo (n=34)-controlled trial of diphenhydramine (n=33) & of dextromethorphan (n=33) in children (2-16.5 yr, median 4.50 yr) with nocturnal cough associated with upper respiratory infection (average illness duration = 4.21±1.57 days before treatment)	Diphenhydramine (salt not specified, but most likely hydrochloride) at 1.25 mg/kg body weight as a single dose 30 minutes before bedtime	Parents' subjective assessment of frequency, severity, & bothersome nature of nocturnal cough of sleep quality for child & parents; also subjective assess-ments by subsets (n=12 for diphen-hydramine; n=13 for placebo) of children (6.2-16.5 yr, median 7.5 yr)	Improvement for all outcomes for all groups; diphenhydramine not superior to placebo in providing nocturnal symptom relief
> 12 years & Adults	Paul et al. 2004; Yoder et al. 2006	[see above]			

A 1-4. **Pharmacokinetic and Efficacy Summaries for OTC Doxylamine**

1. Active Ingredient
   - Name of ingredient: Doxylamine succinate
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	3.75-6.25 mg every 4-6 hr, not to exceed 37.5 mg in 24 hr	7.5-12.5 mg every 4-6 hr, not to exceed 75 mg in 24 hr	"Children 2 to under 6 years of age: oral dosage is 1.9 to 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

No data from pediatric pharmacokinetic studies are available.

5. Efficacy Study Summaries for Doxylamine

These summaries are from published randomized, placebo-controlled studies of doxylamine alone or in combination with other drug active ingredients and a meta-analysis of data from randomized, placebo-controlled studies.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	No studies available				
2 - <6 years	No studies available				
6 - <12 years	No studies available				
> 12 years & Adults	Eccles et al. 1995	Double-blind placebo (n=343)-controlled trial of doxylamine (n=345) in subjects (mean age 25 yr) with colds	Doxylamine succinate 7.5 mg 4 times/day up to 9 doses	Subjects' subjective scoring of runny nose & sneezing 90 min after 2nd & 4th doses	Significantly reduced runny nose & sneezing with doxylamine
	D'Agostino et al. 1998	Meta-analysis of raw data from 8 double-blind placebo-controlled studies, including 6 on doxylamine, to evaluate the effectiveness of antihistamines to reduce the symptoms of runny nose & sneezing over the first 2 days of medication for subjects with common colds that began within 24-48 hr before entry into the study	Doxylamine succinate 7.5 mg 4 times/day	Statistical analysis of data on severity of runny nose & sneezing	Homogeneity of treatment effect across studies & consistency confirmed for pooling the studies; antihistamines shown to be statistically significantly more effective than placebo in reducing severity of runny nose and sneezing

	Thackray 1978	Double-blind crossover controlled trial (n=70) of a combination of doxylamine + ephedrine + dextromethorphan + acetaminophen in subjects (18 – 60 years) with common cold	Doxylamine succinate 7.5 mg + ephedrine sulfate 8 mg + dextromethorphan HBr 15 mg + acetaminophen 600 mg or control syrup in single 30-ml bedtime dose on 2 consecutive nights: one group of 35 (average age 33.2 yr) took active formula 1st night & control syrup on 2nd night, & other group of 35 (average age 34.7 yr) took control syrup 1st night & active formula on 2nd night	Subjects' subjective assessment each morning of relief from symptoms (cough, nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep) & additional-ly on the 2nd morning of which formulation they found to be more effective at relieving global cold symptoms	Significant degree of relief by active formulation compared to control syrup for cough (highly significant difference between groups), nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep; highly significant number of subjects preferred global symptomatic relief from active formulation
	Mizoguchi et al. 2007	Double-blind placebo (n=208)-controlled trial of a combination (n=224) of doxlyamine + dextromethorphan + acetaminophen + ephedrine in subjects (18 – 64 yr, mean 31.3 yr) with common cold symptoms for 1-5 days with at least moderate nasal congestion & a runny nose, at least mild cough, & at least mild pain with one or more of the following: sore throat, sore chest, headache, or body pain/aches	Doxylamine succinate 7.5 mg + dextromethorphan HBr 15 mg + acetaminophen 600 mg + ephedrine sulfate 8 mg in one 30-ml evening dose	Subjects' subjective scoring of symptoms (nasal conges-tion, runny nose, cough, and pain) 3 hr post-dosing and 1 hr after rising the next morning	For primary endpoint (composite of nasal congestion/runny nose/cough/ pain relief scores 3 hr post-dosing), clinically & statistically signifi-cantly greater relief with treatment (p=0.0002); statis-tically significant improve-ment with treatment in each individual symptom score 3 hr post-dosing (p≤0.017); clinically & statistically significant greater benefits on composite score & each of the individual symptoms the next morning in those who had received treatment (p≤0.003)

A 1-5. **Pharmacokinetic and Efficacy Summaries for OTC Phenylephrine**

1. Active Ingredient
   - Name of ingredient: Phenylephrine hydrochloride; phenylephrine bitartrate
   - Pharmacotherapeutic class: Nasal decongestant

2. Indication According to OTC Monograph

   Either of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion," which may be followed by any of the following: "due to" (either) ""the common cold" or "a cold"; "due to" (any one of the following) "hay fever," Hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)."

3. Dosage According to OTC Monograph

	< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
For products containing phenylephrine hydrochloride	"Consult a doctor"	2.5 mg every 4 hr, not to exceed 15 mg in 24 hr	5 mg every 4 hr, not to exceed 30 mg in 24 hr	10 mg every 4 hr, not to exceed 60 mg in 24 hr		"Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor." "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."
For products containing phenylephrine bitartrate	"Ask a doctor"	"Ask a doctor"	7.8 mg every 4 hr, not to exceed 31.2 mg in 24 hr	15.6 mg every 4 hr, not to exceed 62.4 mg in 24 hr		

4. Pharmacokinetic Characteristics

   No data from pediatric pharmacokinetic studies are available.

5. Efficacy Study Summaries for Phenylephrine

These summaries are from published randomized, placebo-controlled studies of phenylephrine alone or in combination with other drug active ingredients and a meta-analysis of data from randomized, placebo-controlled studies

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Hutton et al. 1991	[see below]			
6 months - <6 years	Hutton et al. 1991	Double-blind placebo (n=27)-controlled trial of fixed combination (n=36) of brompheniramine, phenylephrine, & phenylpropanolamine in children (0.5-5 yr, mean 25 ± 15.7 months) with signs of upper respiratory infection (i.e., nasal congestion or rhinorrhea); also a "no treatment" group (n=33)	Fixed combination of brompheniramine maleate (4 mg/5 ml), phenylephrine HCl (5 mg/5 ml), & phenyl-propanolamine HCl (5 mg/5 ml) given 3 times/ day so that brompheniramine dosage was 0.5-0.75 mg/kg body weight/day, which would mean phenylephrine was at 0.625-0.938 mg/kg/day, for 2 days	Parents' subjective assessment of symptoms (congested or runny nose, breathing trouble, fever, cough, decreased appetite, crankiness, sleep disturbance, & excessive sleepiness) at 48 hr	No differences among groups in individual or composite symptom score changes
6 - <12 years	No studies available				
≥12 years & Adults	Cohen 1972	Double-blind trial with single doses of phenylephrine and placebo in 48 subjects with nasal congestion associated with common cold	Phenylephrine 10, 15, & 25 mg one-time single dose	Objective determination of nasal flow/resistance by electronic posterior rhinometry and subjects' subjective estimation of nasal congestion	Decreased nasal flow/ resistance with all 3 doses of phenylephrine, which was apparent at 15 min, maximal between 30 & 90 min, and still present 120 min after treatment
	Kollar et al. 2007	Meta-analysis of the efficacy of a single dose of phenylephrine for relief of nasal congestion associated with common cold (pooled data from 7 placebo-controlled crossover studies; total n=113)	Phenylephrine 10 mg one-time single dose	Calculated change in objectively measured nasal airway resistance	Meta-analysis supports effectiveness of a single oral dose of phenylephrine

A 1-6. **Pharmacokinetic and Efficacy Summaries for OTC Pseudoephedrine**

1. Active Ingredient
   - Name of ingredient: Pseudoephedrine hydrochloride; pseudoephedrine sulfate
   - Pharmacotherapeutic class: Nasal decongestant

2. Indication According to OTC Monograph
   Either of the following: “For the temporary relief of nasal congestion” or “Temporarily relieves nasal congestion,” which may be followed by any of the following: “due to” (either) “”the common cold” or “a cold”; “due to” (any one of the following) “hay fever,” “hay fever (allergic rhinitis),” “hay fever or other upper respiratory allergies,” or “hay fever or other upper respiratory allergies (allergic rhinitis).”

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
“Consult a doctor”	15 mg every 4-6 hr, not to exceed 60 mg in 24 hr	30 mg every 4-6 hr, not to exceed 120 mg in 24 hr	60 mg every 4-6 hr, not to exceed 240 mg in 24 hr		“Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor.” “Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor.”

4. Pharmacokinetic Characteristics

Pseudoephedrine hydrochloride

Publication Reference & Study Characteristics	*Simons et al. 1996;* Single-dose study in 21 children (age 8.8 ± 0.3 yr, weight 32 ± 1 kg); syrup		*Auritt et al. 1981*; Single-dose study in 5 children (age 6 - 12 yr) and 19 adults (age not reported); syrup		Williams et al. 1984.; Single-dose study in 20 healthy male volunteers (age 23.8 ± 5.7 yr, weight 70.4 ± 7.5 kg); syrup
	Children		Children	Adults	Adults
Results:	30 mg dose	60 mg dose	2 mg/kg, 60 mg max.	60 mg dose	60 mg dose
AUC *(ng/mL/hr)*	1260 ± 126	2414 ± 336	*not reported*	*not reported*	1657.7 ± 411.1
t_{max} *(hr)*	2.1 ± 0.3	2.4 ± 0.2	1.86	1.49	1.53 ± 0.91
C_{max} *(ng/mL)*	244 ± 21	492 ± 72	338	211	179.3 ± 24.5
Vd *(L/kg)*	2.6 ± 0.3	2.4 ± 0.4	3.33	2.83	3.4 ± 0.5
$t_{½}$ *(hr)*	3.1 ± 0.5	3.1 ± 0.4	4.61	5.46	5.46 ±1.29
Cl *(mL/min/kg)*	10.3 ± 1.2	9.2 ± 0.7	8.5	6.27	7.7 ± 2.0

5. Efficacy Study Summaries for Pseudoephedrine

These summaries are from published randomized, placebo-controlled studies of pseudoephedrine alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	No studies available				
2 - <6 years	Gallardo et al. 1994	[see below]			
2 - 16 years	Gallardo et al. 1994	Double-blind placebo-controlled trial of pseudo-ehedrine alone (n=15) and in combination (n=20) with naproxen in subjects 2-16 yr with common colds	Every 8 hr for 5 days: 2 – 5 yr pseudoephedrine 15 mg alone or combined with naproxen sodium 50 mg 6 – 9 yr pseudoephedrine 30 mg alone or combined with naproxen sodium 100 mg 10 – 12 mg pseudoephedrine 45 mg alone or combined with naproxen sodium 150 mg 13 – 16 yr pseudoephedrine 60 mg alone or combined with naproxen sodium 200 mg	Physician evaluation of signs & symptoms (nasal discharge, nasal edema, nasal erythema, conjunctival hyperemia, lacrimation, sneezing, guttural voice, fever, nasal congestion, anosmia odynophagia, head-ache, & malaise) initially & after 3rd 7 5th days	Significantly shorter duration of nasal obstruction, mucosal edema, lacrimation, & headache with combi-nation (pseudoephedrine + naproxen); higher symptom relief after 3rd & 5th day with the combination compared to other groups
≥ 12 years & Adults	Bye at al. 1980	Double-blind placebo (n=60)-controlled comparison of pseudo-ephedrine alone (n=61) & in combination with triprolidine (n=55) in adults with common cold	Pseudoephedrine HCl 60 mg, pseudoephedrine HCl 60 mg + triprolidine HCl 2.5 mg, or placebo 3 times/day for as long as participants thought necessary	Subjects' subjective assessment of 12 specified symptoms using a 4-point scale (cold in the head, running nose, sneezing, blocked nose, sore throat, headache, cough, feeling ill, phlegm, hoarseness, ache in back or limps, feeling feverish); overall treatment response	Sneezing, nasal obstruction and overall responses to treatment significantly improved with pseudo-ephedrine & pseudo-ephedrine + triprolidine compared with placebo ($p < 0.01$); other specific symptoms not significantly affected by treatments

	Sperber et al. 1989	Double-blind placebo (n=10)-controlled comparison of pseudo-ephedrine alone (n=23) & in combination with ibuprofen (n=23) in young adults intranasally inoculated with rhinovirus 30 hr before treatment begun	Pseudoephedrine HCl 60 mg, pseuodephedrine HCl 60 mg + ibuprofen 200 mg, or placebo 4 times/day for 4 ½ days (total of 18 doses)	Objective measurement of oral temperature, nasal secretion weights, and nasal patency (rhinometry); subjects' subjective symptom (nose, throat, systemic) scoring	Total symptom scores reduced by 59% by pseudo-ephedrine + ibuprofen and 48% by pseudoephedrine alone, but only nasal symptom scores were substantially different between the groups; significantly less rhinorrhea (nasal secretion weights) in both pseudoephedrine treatment groups; nasal patency most improved in subjects given pseudo-ephedrine + ibuprofen
	Taverner et al. 1999	Double-blind placebo (n=27)-controlled trial of pseudoephedrine (n=25) in subjects with common cold (<5 days) & moderate-to-severe nasal congestion	Pseudoephedrine 60 mg one-time single dose	Objective measurement of nasal cross-sectional area and volume by acoustic rhinometry at 30 min and then every 30 min up to 180 min; subjects' subjective scoring of congestion symptoms	Total nasal minimum cross-sectional area & nasal volume significantly increased by pseudo-ephedrine, with associated reduction in symptom of congestion
	Eccles et al. 2005	Double-blind placebo (n=119)-controlled trial of pseudoephedrine (n=119) in subjects with moderate nasal congestion associated with common cold (<72 hr)	Pseudoephedrine HCl 60 mg 4 times/day for 3 days	Objective measurement of nasal airway resistance by posterior rhinomanometry and objective scoring (visual analogue scale) of nasal congestion every hour for 4 hr after 1st dose on day 1 and after the last dose on day 3	Significantly decreased nasal airway resistance 2-4 hr after 1st dose of pseudoephedrine on day 1 & 0-4 hr after last dose on day 3; lower subjective congestion scores after one dose of pseudoephedrine on day 1 but not after multiple doses on day 3
	Latte & Taverner 2006	Double-blind placebo-controlled trial (n=216) of pseudoephedrine	Pseudoephedrine HCl 60 mg 4 times/day for 3-4 days	Objective measurement of nasal airway resistance by posterior rhinomanometry and objective scoring (visual analogue scale) of symptom severity	Decreased nasal airway resistance and improved symptoms of congestion in subjects taking pseudoephedrine

	Loose & Winkel 2004	Double-blind placebo (n=162)-controlled trial of a combination of pseudo-ephedrine + acetylsalicylic acid (ASA) [see numbers of subjects under "Treatment"] in subjects with nasal congestion associated with common cold; secondarily com-pared effects of pseudoephedrine-ASA combination with those of a combination of pseudoephedrine + acetaminophen	One-time single doses of pseudoephedrine 60 mg + ASA 1,000 mg [n=161]; pseudoephedrine 30 mg + ASA 500 mg [n= 161]; or pseudoephedrine 60 mg + acetaminophen 1,0000 mg [n=159]	Subjects' subjective assessment of nasal congestion, with primary efficacy variable being area under the curve for differences from baseline on a nasal congestion scale in first 2 hr after treatment	All active treatments statistically significantly superior to placebo; combination of pseudo-ephedrine 60 mg + ASA 1,000 mg shown efficacious for all subjects for entire 6 hr, with significant results for nasal congestion & relief of nasal stuffiness
	Berkowitz et al. 1989	Double-blind placebo (n=141)-controlled trial of a combination of pseudo-ephedrine + loratadine (n= 142) in subjects with common cold	Pseudoephedrine 120 mg + loratadine 5 mg 2 times/day for 5 days	Physician assessment of overall response and evaluation of severity scores for rhinorrhea, nasal patency, & swelling on days 3 & 5; subjects' subjective scoring of overall response and symptoms	Evaluations by both subjects & physicians suggest superiority of the pseudoephedrine-loratadine combination over placebo in relieving symptoms, including nasal congestion, sneezing, postnasal drain-age, and nasal discharge
	Gallardo et al. 1994	[see above]			
	Blanco de la Mora et al. 2000	Double-blind placebo-controlled trial of a combination of pseudo-ephedrine + loratadine + acetaminophen (total n=40)	Pseudoephedrine 60 mg + loratadine 2.5 mg + acetaminophen 500 mg [per tablet or in 2 tablets?], 2 tablets every 12 hr for 5 days	Investigator subjective assessment of nasal congestion, rhinorrhea, & general malaise on days 3 & 5; subjects' subjective evaluation of symptoms	Significant difference between treatment groups on 3rd treatment day; a favorable effect on edema of nasal mucosa & significant reduction of rhinorrhea on 3rd day with drug treatment

	Curley et al. 1988	Double-blind placebo (n=35, 28.1±5.2 yr)-controlled trial of a combination (n=38, 33.7±8.8 yr) of pseudoephedrine + dexbrompheniramine in subjects (>18 yr) with symptoms of common cold (12 -72 hr)	Pseudoephedrine sulfate at 120 mg + dexbromphenir-amine maleate at 6 mg 2 times/day for 7 days	Objective pulmonary function testing (spirometry & flow-volume loops) initially & on 4th, 8th, & 14th day; subjects' subjective daily assessment of severity of 17 symptoms (including cough, nasal obstruction, nasal discharge, postnasal drip, throat-clearing, sneezing, sore throat) for 14 days	Reduced postnasal drip & significantly decreased severity of cough, nasal obstruction, nasal discharge, & throat-clearing during first few days with treatment: significantly lower mean severity ranking of cough on 3rd, 4th, & 5th days ($p \leq 0.05$), of nasal discharge on 2nd ($p \leq 0.05$) & 3rd ($p \leq 0.01$) days, of nasal obstruction on 2nd, 3rd ($p \leq 0.01$), 4th ($p \leq 0.05$), & 5th ($p \leq 0.01$) days, & of throat-clearing on 2nd & 3rd days ($p \leq 0.01$); in pulmonary function testing, cough significantly asso-ciated only with presence of extrathoracic, upper airway obstruction identified by inspiratory flow rates

A 1-7. **Pharmacokinetic and Efficacy Summaries for OTC Dextromethorphan**

1. Active Ingredient
   - Name of ingredient: Dextromethorphan; dextromethorphan hydrobromide
   - Pharmacotherapeutic class: Antitussive (cough suppressant)

2. Indication According to OTC Monograph
   "Temporarily" (any one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough due to" (either of the following: "minor bronchial irritation" or "minor throat and bronchial irritation") (either of the following: "a cold" or "the common cold") "or inhaled irritants." or
   "Temporarily" (any one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough (any one of the following: "as may occur with," "associated with," or "occurring with") (any one of the following: "a cold," "the common cold," or "inhaled irritants.")

3. Dosage* According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	2.5-5 mg every 4 hr or 7.5 mg every 6-8 hr, not to exceed 30 mg in 24 hr, "or as directed by a doctor."	5-10 mg every 4 hr or 15 mg every 6-8 hr, not to exceed 60 mg in 24 hr, "or as directed by a doctor."	10-20 mg every 4 hr or 30 mg every 6-8 hr, not to exceed 120 mg in 24 hr, "or as directed by a doctor."		"Do not use in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving the product."

*Equivalent to dextromethorphan hydrobromide

4. Pharmacokinetic Characteristics

Dextromethorphan hydrobromide

Publication Reference & Study Characteristics	*Schmitt et al. 1997;* Multiple-dose study in 6 children (age 6 - 35 mo, weight 5.6 -11.7 kg); oral solution by naso-gastric tube		*Woodworth et al. 1987;* Multiple-dose study in 24 male healthy volunteers; immediate-release (IR) and controlled-release (CR) oral solution	
	Children*		Adults**	
Results:	0.5 mg/kg every 6 hours starting 24 hr before surgery, followed by 10 mg/kg at intubation but before surgery and 10 mg/kg immediately after the end of surgery. Thereafter, 8 mg/kg every 6 hr until 48 hr post surgery (7 x 8 mg/kg), followed by stepwise weaning over another 48 h (4 x 4 mg/kg, 2x2 mg/kg, 2x1 mg/kg)		30 mg 4 x daily (IR) or 60 mg 2 x daily (CR) for 2 weeks	
Plasma levels *(ng/mL)*	Dextromethorphan *after 7 x 8 mg/kg at 6 hr intervals*	Free Dextrorphan *after 7 x 8 mg/kg at 6 hr intervals*	Dextromethorphan Cmax at steady state	Free Dextrorphan Cmax at steady state
	550 – 1600 estimated from published plasma concentration figures	75 – 500 estimated from published plasma concentration figures	205.5 ± 134.9 (IR) 198.0 ± 139.0 (CR)	152.6 ± 110.1 (IR) 173.1 ± 152.9 (CR)

* DXM used experimentally to investigate its protective effect towards cerebral injury in children undergoing cardiac surgery with cardiopulmonary bypass.
** 10 subjects were intermediate and 14 were slow DXM metabolizers.

5. Efficacy Study Summaries for Dextromethorphan

These summaries are from published randomized, placebo-controlled studies of dextromethorphan alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Taylor et al. 1993	[see below]			
	Korppi et al. 1991	[see below]			
	Reece et al. 1966	[see below]			
2 - <6 years	Taylor et al. 1993	[see below]			
	Paul et al. 2004	[see below]			
	Korppi et al. 1991	[see below]			

≤12 years	Taylor et al.1993	Double-blind placebo (n=13)-controlled comparison of a guaifenesin & dextromethorphan combination (n=19) & a guaifenesin & codeine combination (n=17) in children (18 mo – 12 yr, mean 4.7 ± 2.3 yr) with night cough less than 14 days in duration	Single dose at bedtime on 3 consecutive nights: 18 mo – 5 yr, in 2.5 ml 50 mg guaifenesin combined with 7.5 mg dextromethorphan or with 5 mg codeine 6 – 12 years, in 5 ml 100 mg guaifenesin combined with 15 mg dextromethorphan or with 10 mg codeine	Subjective ratings in the mornings by parents on the amount of coughing, loss of sleep because of coughing, and any noticed posttussive emesis during the previous night; cough scores and composite symptom scores (total of cough score + loss-of-sleep score + posttussive-emesis score) calculated and mean reductions analyzed	Neither combination (guaifenesin + dextro-methorphan nor guaifenesin + codeine) was superior in treating night cough in children.
	Paul et al. 2004	[see below]			
	Korppi et al. 1991	Placebo (n=26)-controlled trial of dextromethorphan (n=24) & of a combination of dextromethorphan + salbutamol in children (1-10 yr, mean 3.8 yr) with cough associated with acute respiratory infection	Dextromethorphan HBr at 1.5 mg/ml with or without salbutamol at 0.2 mg/ml: 5 ml to children <7 yr & 10 ml to those ≥7 yr, 3 times/day for 3 days	Parents' subjective daily scoring of symptoms (frequency & severity of nocturnal cough, frequency & severity of daytime cough) & their daily assessment of child's general condition & end-of-treatment evaluation of overall benefit of medication	Symptom scores dropped significantly in all 3 groups, but no difference between groups for symptom scores nor in reported general conditions on any of the 3 days; marked relief reported for more than half of the patients (56% with dextromethorphan, 66% with combination, & 73% with placebo)

	Reece et al. 1966	Placebo (n=7)-controlled trial of 2 dextromethorphan-containing multi-ingredient antitussives* in children (2 mo -9 yr) hospitalized with respiratory illness & having the symptom of coughing * Two formulations containing in each 5 ml: 1st formulation (n=7) dextromethorphan HBr 15 mg + phenyl-propanolamine HCl 12.5 mg + pheniramine maleate 6.25 mg + pyrilamine maleate 6.25 mg + ammonium Cl 90 mg 2nd formulation (n=8) dextromethorphan HBr 7.5 mg + phenylpropanolamine HCl 8.75 mg + glyceryl guaiacolate 37.5 mg + alcohol 5%	See formulations in preceding column to the left. Every 8 hr, for a total of 5 doses, including each day's last dose being at bedtime: <2 yr 1st formulation: 1.25 ml 2nd formulation: 2.5 ml [equal content of dextromethorphan at 3.75 mg] 2 – 6 yr 1st formulation: 2.5 ml 2nd formulation: 5.0 ml [equal content of dextromethorphan at 7.5 mg] >7 yr 1st formulation: 5.0 ml 2nd formulation: 10 ml [equal content of dextromethorphan at 15 mg] Placebo given in same volumes as for 2nd formulation	Objective evaluation of 8-hr nighttime cough counts (total & in 2-hr increments) from tape recording through a microphone above subject's bed	Both dextromethorphan-containing formulations were more effective than placebo in suppressing cough, with 47% decrease in total 8-hr cough count with the 1st formulation & 37% decrease with the 2nd vs. 15% decrease with placebo

	Reece et al. 1966	Placebo (n=14)-controlled trial of 2 dextromethorphan-containing multi-ingredient antitussives* in children (2 mo – 12 yr, average 3.6 yr) with cough but without chronic respiratory illness * Two formulations containing in each 5 ml: 1st formulation (n=16) dextromethorphan HBr 15 mg + phenyl-propanolamine HCl 12.5 mg + pheniramine maleate 6.25 mg + pyrilamine maleate 6.25 mg + ammonium Cl 90 mg 2nd formulation (n=13) dextromethorphan HBr 7.5 mg + phenylpropanolamine HCL 8.75 mg + glyceryl guaiacolate 37.5 mg + alcohol 5%	Dosage, treatment frequency, & treatment duration unclear	Mothers' subjective assessment of treatment effect and duration of action in stopping cough or reducing frequency of cough recorded on a standard form	Satisfactory antitussive effect reported for all groups, but dextromethorphan-containing formulations were shown to be statistically significantly more effective than placebo in suppressing cough; cough suppressant effect of 46%-56% vs. 21% with placebo

2 – 16.5 years	Paul et al. 2004; Yoder et al. 2006	Double-blind placebo (n=34)-controlled trial of dextromethorphan (n=33) & of diphenhydramine (n=33) in children (2-16.5 yr, mean 4.50 yr) with nocturnal cough associated with upper respiratory infection (average illness duration = 4.21±1.57 days before treatment)	Dextromethorphan (no salt specified) 7.5 mg to 2- to 5-yr-olds, 15 mg to 6- to 11-yr-olds, & 30 mg to those ≥12 years old	Parents' subjective assessment of frequency, severity, & bothersome nature of nocturnal cough of sleep quality for child & parents; also subjective assessments by subsets (n=12 for dextromethorphan; n=13 for placebo) of children (6.2-16.5 yr, median 7.5 yr)	Improvement for all outcomes for all groups; dextromethorphan not superior to placebo in providing nocturnal symptom relief
	Taylor et al. 1993	[see above]			
≥ 12 years & Adults	Tukiainen et al. 1986	Double-blind placebo (n=34)-controlled comparison of dextromethorphan (n=36) & a dextromethorphan-salbutamol combination (n=38) in out-patients who had an acute respiratory infection with cough	Dextromethorphan 30 mg, dextromethorphan 30 mg + salbutamol 2 mg, or placebo 3 times/day for 4 days	Subjects' subjective scoring of daytime cough frequency & severity and nighttime cough severity & breathlessness; objective measurement of sputum quantity; subjective(?) assessment of ease of expectoration	No statistically significant differences between treatments for symptom scores for daytime cough frequency & severity, sputum quantity or ease of expectoration; combination superior in suppressing nighttime cough, although improvement in all groups during the 4-day treatment period; significant improvement in daytime cough in all groups

	Parvez et al. 1996	Three double-blind placebo-controlled trials (n = 108, 134, & 209) of a single dose of dextromethorphan for acute cough due to acute upper respiratory infection (non-streptococcal); total of 451 subjects	Dextromethorphan 30 mg one-time single dose	Objective quantitative evaluation with a multi-dimensional cough measurement system (microphone & digitized data); subjective patient assessments of cough and rating of troublesomeness of cough	Consistently showed significantly reduced cough counts & total effort, with increased rest periods & unchanged average intensity per cough bout with dextro-methorphan; no treatment effect on subjective assessments with visual analog scale in two studies; in the third study, trend toward improvement in global assessment of cough with dextromethorphan at 120 min & dextromethor-phan shown in ratings of troublesomeness of cough to be significantly superior at 120 min
	Lee et al. 2000	Double-blind placebo (n=22)-controlled trial of a single dose of dextromethorphan (n=21) for subjects (18-46 yr, mean 22.9 yr) with acute cough associated with upper respiratory infection	Dextromethorphan 30 mg one-time single dose	Objective recording of cough frequency (CF) and cough sound pressure level (CSPL); subjective patient assessments of cough severity	Similar trends in dextro-methorphan & placebo groups with statistically significant reductions in CSPL, CF, & subjective scores (but no significant difference between groups); statistically significant greater reduction in mean CSPL from baseline to 90 min with dextromethorphan, but the difference in mean CSPL changes between the 2 groups not significant from baseline to 135 min & to 180 min.

	Pavesi et al. 2001	Meta-analysis of six double-blind placebo (n=354)-controlled clinical trials (may include studies reported by Parvez et al. 1996) of a single dose of dextro-methorphan (n=356) for acute cough due to uncomplicated upper respiratory infections	Dextromethorphan 30 mg one-time single dose	Objective recording continuously for 3 hr after treatment, measuring cough bouts, cough components, cough effort, cough intensity, and cough latency	Meta-analysis showed consistent results across most of the studies for each of the efficacy variables; significantly greater reductions in cough bouts, cough components, and cough effort and an increase in cough latency with dextromethorphan
	Paul et al. 2004; Yoder et al. 2006	[see above]			
	Thackray 1978	Double-blind crossover controlled trial (n=70) of a combination of dextromethorphan + acetaminophen + ephedrine + doxylamine in subjects (18 – 60 yr) with common cold	Dextromethorphan HBr 15 mg + acetaminophen 600 mg + ephedrine sulfate 8 mg + doxylamine succinate 7.5 mg or control syrup in single 30-ml bedtime dose on 2 consecutive nights: one group of 35 (average age 33.2 yr) took active formula 1st night & control syrup on 2nd night, & other group of 35 (average age 34.7 yr) took control syrup 1st night & active formula on 2nd night	Subjects' subjective assessment each morning of relief from symptoms (cough, nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep) & additionally on the 2nd morning of which formulation they found to be more effective at relieving global cold symptoms	Significant degree of relief by active formulation compared to control syrup for cough (highly significant difference between groups), nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep; highly significant number of subjects preferred global symptomatic relief from active formulation

	Mizoguchi et al. 2007	Double-blind placebo (n=208)-controlled trial of a combination (n=224) of dextromethorphan + doxlyamine + acetaminophen + ephedrine in subjects (18 – 64 yr, mean 31.3 yr) with common cold symptoms for 1-5 days with at least moderate nasal congestion & a runny nose, at least mild cough, & at least mild pain with one or more of the following: sore throat, sore chest, headache, or body pain/aches	Dextromethorphan HBr 15 mg + doxylamine succinate 7.5 mg + acetaminophen 600 mg + ephedrine sulfate 8 mg in one 30-ml evening dose	Subjects' subjective scoring of symptoms (nasal congestion, runny nose, cough, and pain) 3 hr post-dosing and 1 hr after rising the next morning	For primary endpoint (composite of nasal congestion/runny nose/cough/ pain relief scores 3 hr post-dosing), clinically & statistically significantly greater relief with treatment ($p=0.0002$); statistically significant improvement with treatment in each individual symptom score 3 hr post-dosing ($p\leq0.017$); clinically & statistically significant greater benefits on composite score & each of the individual symptoms the next morning in those who had received treatment ($p\leq0.003$)
	Galvez 1985	Double-blind placebo (n=32)-controlled trial of a combination (n=28) of dextromethorphan + pseudoehedrine + azatadine in subjects (12 – 70 yr) with common cold & associated cough, nasal congestion, & rhinorrhea	Dextromethorphan HBr 20 mg + pseudoephedrine sulfate 60 mg + azatadine maleate 1 mg in 5 ml 3 times/day for 5 days	Subjective assessment (4-point scale) by physician (in consultation with subjects) of rhinorrhea, nasal congestion, cough, sneezing, postnasal drip, lacrimation, headache, tiredness/drowsiness, & general achiness the 1st day (before dose) & on 3rd & 5th days	More rapid & complete relief of nasal congestion & cough with treatment; excellent or good thera-peutic responses at interim ($p\leq0.01$) & final ($p<0.01$) evaluations in statistically greater number of subjects with treatment, & faster onset of symptommatic relief (reported at 12 hr by 55% treated subjects vs. 17% with placebo); excellent or good overall responses by 3rd day in 60% of treated vs. 8% of placebo subjects, & by 5th day in 77% of treated vs. 21% with placebo

	Scavino 1985	Double-blind placebo (n=29)-controlled trial of a combination (n=29) of dextro-methorphan + doxlyamine + acetaminophen + ephedrine in subjects (12-66 years) with common cold & associated cough (symptomatic 24-48 hr before enrollment)	Dextromethorphan HBr 20 mg + pseudoephedrine sulfate 60 mg + azatadine maleate 1 mg in 5 ml 3 times/day for 5 days	Subjective assessment (4-point scale) by physician of symptoms (in consultation with subjects: rhinorrhea, nasal congestion, cough, sneezing, postnasal drip, & lacrimation) & signs (swelling & hyperemia of nasopharyngeal mucosa, nasal secretions, & hyperemia) the 1st day (before dose) & on 3rd & 5th days; physician evaluation of overall therapeutic response on 3rd & 5th days	Statistically significantly more reduction in symptom severity scores at interim ($p<0.01$) & final evaluations ($p<0.01$) with treatment (59% improvement vs. 33% with placebo on 3rd day; 92% vs. 69% on 5th day), as well as faster onset of symptomatic relief (reported at 12 hr or less by 40% of treated subjects vs. none with placebo; more rapid improvement (lessened severity) in signs with treatment, & statistically significant difference ($p<0.01$) (57% improvement vs. 30% with placebo on 3rd day; 93% vs. 73% on 5th day); excellent or good overall therapeutic responses by 3rd day in 76% of treated subjects vs. 17% of placebo group, & by 5th day in 88% of treated vs. 48% with placebo

A 1-8. **Pharmacokinetic and Efficacy Summaries for OTC Guaifenesin**

1. Active Ingredient
   - Name of ingredient: Guaifenesin
   - Pharmacotherapeutic class: Expectorant

2. Indication According to OTC Monograph
   "Helps loosen phlegm (mucus) and thin bronchial secretions to" (one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive").

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	50-100 mg every 4 hr, not to exceed 600 mg in 24 hr [NDA products say "children under 12 years of age: do not use"]	100-200 mg every 4 hr, not to exceed 1,200 mg in 24 hr [NDA products say "children under 12 years of age: do not use"]	200–400 mg every 4 hr, not to exceed 2,400 mg in 24 hr	"Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis."	For products labeled only for children < 6 yr: "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

4. Pharmacokinetic Characteristics

   No data from pediatric pharmacokinetic studies are available.

5. Efficacy Study Summaries for Guaifenesin

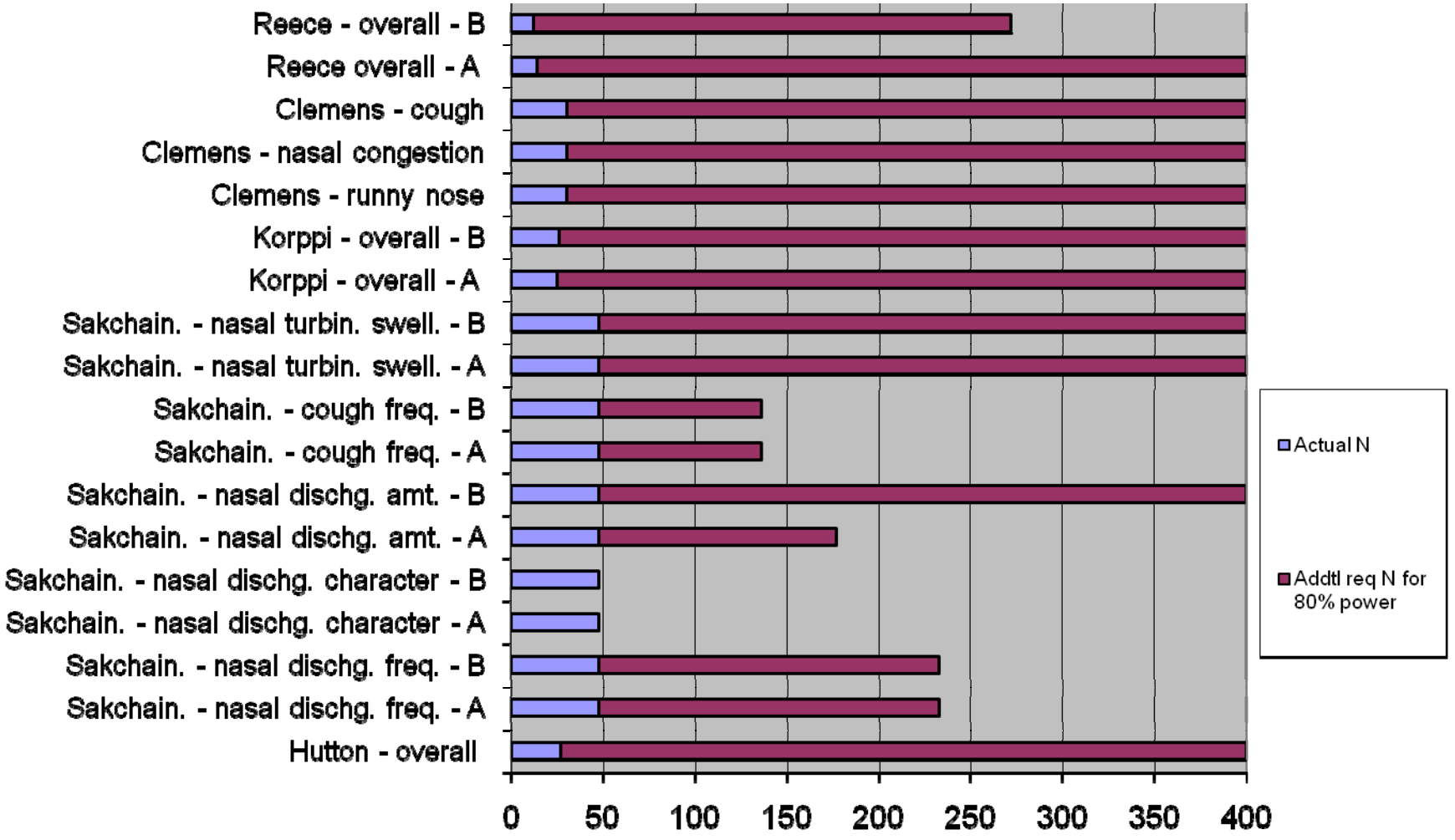
These summaries are from published randomized, placebo-controlled studies of guaifenesin alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Taylor et al. 1993	[See below]			
2 - <6 years	Taylor et al. 1993	[See below]			
18 months - ≤12 years	Taylor et al. 1993	Double-blind placebo (n=13)-controlled comparison of a guaifenesin & dextromethorphan combination (n=19) & a guaifenesin & codeine combination (n=17) in children (18 mo- 12 yr, mean age 4.7±2.3 yr) with night cough less than 14 days in duration	Single dose at bedtime on 3 consecutive nights: 18 mo – 5 yr, in 2.5 ml 50 mg guaifenesin combined with 7.5 mg dextromethorphan or with 5 mg codeine 6 – 12 yr, in 5 ml 100 mg guaifenesin combined with 15 mg dextromethorphan or with 10 mg codeine	Subjective ratings in the mornings by parents on the amount of coughing, loss of sleep because of coughing, and any noticed posttussive emesis during the previous night; cough scores and composite symptom scores (total of cough score + loss-of-sleep score + posttussive-emesis score) calculated and mean reductions analyzed	Neither combination (guaifenesin + dextro-methorphan nor guaifenesin + codeine) superior in treating night cough in children
> 12 years & Adults	Robinson et al. 1977	Double-blind multi-investigator placebo (n=121)-controlled trial of guaifenesin (n=118) in subjects, >18 years, with moderate to severe cough associated with upper respiratory infection	200 mg guaifenesin (in 10 ml) 4 times/day for 3 days	Subjective rating by subjects initially and at 24, 48, and 72 hr; physician evaluation initially & at 72 hr; objective measure of sputum characteristics	Guaifenesin significantly reduced cough frequency, cough intensity, and chest discomfort in subjects with initial nonproductive and productive cough and significantly increased sputum volume and facilitated raising sputum in subjects with initial productive cough.

	Kuhn et al. 1982	Double-blind placebo (n=32)-controlled trial of guaifenesin (n=33) in subjects, 18-30 years, with acute respiratory illness of less than 48 hours' duration with cough	400 mg guaifenesin in 30ml every 6 hr for 30 hr (total of 2,400 mg)	Objective recorded cough counting for 42 subjects during 24-hr baseline & 36-hr treatment periods; subjective rating by subjects on frequency of cough, cough severity, cough discomfort, chest discomfort, sputum quantity, & sputum thickness	Guaifenesin showed no antitussive effect but was associated with a perceived decrease in sputum quantity & a reduction in sputum thickness.
	Parvez et al. 1996	Double-blind placebo (n=29)-controlled trial of guaifenesin (n=31) in adults with chronic cough	1200 mg/day guaifenesin for 14 days	Sputum collected, weighed and volume measured. Sputum concentrations of a sputum glycoprotein marker, fucose, were also measured. Objective recording of cough; Subjective patient assessment of ease of expectoration	GUA-treated patients maintained a steady sputum volume output over the study period with a significant difference to placebo of 37% on day 14. Fucose was significantly reduced in the GUA vs the placebo group on day 14. A subgroup of high sputum producers (>40mL pre-treatment) reported a large and significant improvement in ease of expectoration. GUA also produced larger reductions in average intensity per cough compared to placebo on days 4 and 7 which was statistically significant on day 4 ($p<0.05$).

Appendix 2. *Post hoc* Statistical Analysis of 8 Pediatric Clinical Trials

Sample sizes necessary to achieve statistical significance at 80% power based on effect size observed in pediatric studies



If a study has two comparators, they are distinguished by the letter after the lead author's name.

Data from 8 published pediatric randomized controlled trials, with calculation of the sample size required to achieve statistical significance at 80% based on the power (page 1 of 2)

Article (active/placebo group sample sizes)	**Relevant endpoint**	**Observed difference from placebo (+ values indicative of efficacy) (within-group size reqd for the difference to be significant*)**	**Standard deviation (S) or relevant related data[1]**	**True difference that is detectable with 80% power**	**Clinically meaningful difference cited in article / Power / within-grp size reqd for 80% power**
Hutton et al (30/24)	a) % subjects improved overall b) Relative amt of improvement (averaged across 9 symptoms on standardized scales)	a) -4% b) -0.10	a) Placebo improvement rate: 71% b) S = 0.506[3]	a) 29% b) 0.40	a) NP[2] b) NP
Sakchainanont el al (48/48/47) (2 active groups)	% subjects improved: a) nasal discharge frequency b) nasal discharge character c) nasal discharge amount d) cough frequency e) nasal turbinate swelling	Act. 1 / Act. 2 a) 9% (233) / 13% (113) b) 30% (28) / 30% (28) c) 12% (177) / 7% (421) d) 12% (136) / 12% (136) e) 2% (3396) / -3%	Placebo improvement rate[4] : a) 62% b) 43% c) 47% d) 28% e) 21%	 a) 27% b) 30% c) 30% d) 30% e) 29%	NP
Yoder et al (12/12/13) (2 active groups)	a) Chg from baseline (BL) of a cough frequency assessment on a 0-6 scale b) Sum of chg from BL of four cough assessments, each on a 0-6 scale	a) Active 1: 0.20 (505) Active 2: 0.37 (149) b) Active 1: 4.04 (27) Active 2: 0.13 (25,000)	a) S = 1.62[3] b) S = 7.38[3]	a) 1.90 b) 8.64	a) 1 unit / 32% / 43 b) NP
Taylor et al (19/13) (only DM active group considered)	Chg from BL of a cough assessment on a 0-4 scale	NA	NP[5]	NA	NA
Paul et al (33/33/34) (2 active groups)	a) Chg from BL of a cough frequency assessment on a 0-6 scale b) Sum of chg from BL of five cough assessments, each on a 0-6 scale	a) Active 1: -0.27 Active 2: -0.27 b) Active 1: 0.94 (450) Active 2: -0.79	a) S = 1.18[3] b) S = 7.18[3]	a) 0.82 b) 4.99	a) 1 unit / 93% / 23 b) NP

Data from 8 published pediatric randomized controlled trials, with calculation of the sample size required to achieve statistical significance at 80% based on the power (page 2 of 2)

Korppi et al (25/24/26) (2 active groups)	a) Sum of chg from BL of four cough assessments, each on a 0-3 scale b) General condition on a 0-3 scale c) % subjects improved	a) NA b) NA c) Active 1: -16% Active 2: 5% (503) [based on 22/19/24 subjects]	a) NP b) NP c) Placebo improvement rate: 79% (based on 24 subjects)	a) NA b) NA c) No value exists[6]	NP
Clemens et al (28/31)	a) Relief of various cold symptoms, each assessed on a 0-6 scale b) % subjects improved: i) runny nose ii) nasal congestion iii) cough	a) NA b) i) -8% ii) -2% iii) 8% (563)	a) NP b) Placebo % improvement rates[7]: i) 58 ii) 51 iii) 43	a) NA b) i) 34% ii) 36% iii) 38%	a) NA b) NP
Reece et al (7/8/7 in inpatient study; 16/13/14 in ambulatory study) (2 active groups)	a) Chg from BL in total daily cough count (inpatient study) b) % subjects with satisfactory response (ambulatory study)	a) Active 1: 59.1 (20) Active 2: 72.0 (14) b) Active 1: 7% (481) Active 2: 8% (272) [based on 15/12/12 subjects]	a) S = 92.5[8] b) Placebo % improvement rate: 67 (based on 12 subjects)	a) 150.9/145.1[9] b) No value exists[6]	NP

NP: Not provided (insufficient information)
NA: Not applicable since power calculations cannot be done
*: Computed only when active treatment is numerically superior to placebo

[1] Power calculations depend on the standard deviation under the null hypothesis (active ineffective). With dichotomous data, such as % of subjects improved, this standard deviation is related to the average of the within-group improvement rates, and under the null hypothesis, the active improvement rate is the same as the placebo rate.

[2] Article cited as meaningful that the percent of subjects receiving active treatment be 28% higher than no treatment. But the meaningful difference should be versus placebo since large placebo effects are typically seen in these studies.

[3] Computed from the observed means and overall p-values provided in the article

[4] Percentages of subjects with a worsened or unchanged condition were combined for calculations.

[5] The within-day data were analyzed non-parametrically (Mann-Whitney tests) for which the provided p-values are insufficient for power calculations. Sometimes the non-parametric p-values can be assumed to be close to the parametric ones and thus could be used for the power calculations; unfortunately an examination of the observed means and p-values here suggest that the non-parametric p-values would be poor estimates of the parametric ones.

[6] Even if the active improvement rate is 100%, this study cannot detect a significant difference with 80% power.

[7] These rates assume that within each group the % of subjects improving is the same as the % of reports of improvement, which appear in the article.

[8] Computed from the raw data provided in article

[9] Detectable differences versus placebo for Active 1/Active 2; value slightly smaller for Active 2 due to its slightly larger sample size

Appendix 3. Supportive Tables for Section 4 (Pharmacokinetics)

Appendix 3. Supportive Tables for Section 4 (Pharmacokinetics)

Available Pseudoephedrine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for pseudoephedrine in 119 children ages 2 through 11 years old were collected from a multiple-dose study [McNeil 1999], two published single-dose studies [Auritt 1981, Simons 1996], and three single-dose studies for pediatric cold/allergy/sinus OTC products [Wyeth 2002a, Wyeth 2004]. FDA had summarized data for the latter studies as part of the basis of approval for new drug applications, NDA 21-373 and 21-587, and these summaries are publicly available per the Freedom of Information Act. The dose-independent pharmacokinetic parameters, oral clearance CL/F, half-life t½, and apparent distribution volume Vd/F from studies in children and adults are listed in Table 4.5; whereas, the doses and drug exposure parameters (AUC_{INF} and C_{MAX}) are listed in Table 4.6.

Table 4.5 Dose-Independent Pharmacokinetic Parameters (Mean, cv%) for Pseudoephedrine by Age Group

Age Group (Study Reference)	n	Age (y)	t ½ (h)	CL/F (mL/kg/min)	Vd/F (L/kg)
Adults 18 to 45 years	***147***	***28***	***6.3***	***6.5***	***3.3***
McNeil 1987 (Study 87-744)	24	29 ± 5.1	7.0 (20%)	6.4 (36%)	3.7 (17%)
McNeil 1992 (Study 91-104)	12	27 ± 7.3	6.4 (33%)	5.5 (28%)	2.8 (15%)
McNeil 1993 (Study 91-107)	24	30 ± 8.3	5.8 (19%)	7.5 (36%)	3.7 (19%)
Wyeth 2004 (Study AR-00-02)	26	28	5.5 (19%)	7.0 (NR).	NR
Auritt 1981	19	NR	5.5 (NR)	6.3 (NR).	2.8 (NR).
Williams 1984	18	24 ± 5.7	5.6 (19%)	7.3 (25%)	3.3 (12%)
Yacobi 1980	24	19 to 41	7.9 (21%)	5.2 (26%)	3.5 (32%)
Children 6 to < 12 years	***124***	***8.9***	***4.0***	***10.2***	***3.2***
McNeil 1999 (Study 97-024)	19	9.0 ± 1.8	3.3 (17%)	12.7 (17%)	3.5 (20%)
Wyeth 2002a (Study AQ-99-02)[a]	28	8.6 ± 1.6	3.9 (9%)	10.0 (20%)	3.4 (19%)
Wyeth 2002a (Study AQ-99-02)[a]	28	8.6 ± 1.6	4.9 (11%)	NR	NR
Wyeth 2004 (Study AR-00-03)	30	9.0	4.2 (15%)	9.3 (NR).	NR
Auritt 1981	5	NR	4.6 (NR)	8.5 (NR)	3.3 (NR).
Simons 1996[b]	7	8.8 ± 0.3	3.1 (16%)	10.3 (28%)	2.6 (12%)
Simons 1996[b]	7	8.8 ± 0.3	3.1 (13%)	9.2 (8%)	2.4 (17%)
Children 2 to < 6 years	***23***	***3.9***	***4.8***	***11.4***	***4.0***
McNeil 1999 (Study 97-024)	4	5.0 ± 0.7	3.8 (29%)	11.4 (21%)	3.6 (9%)
Wyeth 2002a (Study AQ-00-04)[c]	9	3.8 ± 1.2	4.7 (34%)	11.4 (34%)	4.2 (21%)
Wyeth 2002a (Study AQ-00-04)[c]	10	3.6 ± 1.3	5.3 (36%)	NR	NR

a: crossover study with 28 children; b: parallel-group study with 7 and 7 children, ages reported for all enrolled subjects; c: parallel-group study with 9 and 10 children; NR = not reported.

Table 4.6 Dose-Dependent Pharmacokinetic Parameters[a] (Mean, cv%) for Pseudoephedrine by Age Group

Age Group (Study Reference)	n	Age (y)	Form - C or S	Dose (mg)	AUC_{INF} (ng·h/mL)	AUCtau (ng·h/mL)	C_{MAX} (ng/mL)	T_{MAX} (h)
Adults 18 to 45 years	***139***	***27***	***---***	***60***	***1993***	***---***	***215***	***1.74***
McNeil 1992 (Study 91-104)	12	27 ± 7.3	Tablet-S	60	2594 (28%)	NA	232 (30%)	1.96 (32%)
Wyeth 2002b (Study AD-99-01)	28	26	Tablet-S	60	1801 (25%)	NA	231 (25%)	1.71 (42%)
Wyeth 2002b (Study AD-99-03)	12	30	Tablet-C	60	2066 (22%)	NA	224 (22%)	1.52 (39%)
Wyeth 2004 (Study AR-00-02)	26	28	Liquid-C	60	2085 (20%)	NA	211 (17%)	1.80 (33%)
Auritt 1981	19	NR	Liquid-S	60	NR	NA	211 (NR)	1.49 (NR)
Williams 1984	18	24 ± 5.7	Tablet-S	60	1712 (21%)	NA	180 (17%)	1.94 (44%)
Yacobi 1980	24	19 to 41	Tablet-C	30 x 60	NA	2323 (24%)	NA	NA
Children 6 to < 12 years	***112***	***8.9***	***---***	***31***	***1715***	***---***	***212***	***1.85***
McNeil 1999 (Study 97-024)	19	9.0 ± 1.8	Liquid-C	5 x 35 [b]	NA	1248 (21%)	214 (19%)	1.81 (28%)
Wyeth 2002a (Study AQ-99-02)[c]	28	8.6 ± 1.6	Liquid-C	30	1735 (27%)	NA	218 (24%)	1.87 (43%)
Wyeth 2002a (Study AQ-99-02)[c]	28	8.6 ± 1.6	Liquid-S	30	1767 (32%)	NA	215 (23%)	1.80 (42%)
Wyeth 2004 (Study AR-00-03)	30	9.0	Liquid-C	30	1755 (29%)	NA	195 (24%)	1.85 (35%)
Simons 1996	7	8.8 ± 0.3	Liquid-S	30	1260 (25%)	NA	244 (21%)	2.1 (33%)
Children 2 to < 6 years	***23***	***3.9***	***---***	***16***	***1325***	***---***	***183***	***1.32***
McNeil 1999 (Study 97-024)	4	5.0 ± 0.7	Liquid-C	5 x 20 [b]	NA	1302 (27%)	230 (10%)	1.22 (34%)
Wyeth 2002a (Study AQ-00-04)[d]	9	3.8 ± 1.2	Liquid-C	15	1292 (41%)	NA	179 (17%)	1.21 (69%)
Wyeth 2002a (Study AQ-00-04)[d]	10	3.6 ± 1.3	Liquid-S	15	1355 (41%)	NA	167 (27%)	1.46 (47%)

a: Except T_{MAX}, which is not a dose-dependent parameter, but which is usually reported with C_{MAX}.

b: Dosing regimen for the multiple-dose study of pseudoephedrine 1.125 mg/kg administered every six hours for five doses. The average milligram dose is listed. Both C_{MAX} and T_{MAX} are modeled estimates for the first single dose, whereas AUCtau is the area under curve for the dosing interval (tau) at steady state, which is equivalent to AUC_{INF}.

c: crossover study with 28 children

d: parallel-group study with 9 and 10 children

Key: NA – not applicable; NR – not reported; C – combination pseudoephedrine product; S – single ingredient pseudoephedrine.

Available Chlorpheniramine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for chlorpheniramine in 41 children ages 6 through 11 years old were collected from a published study [Simons 1982] and a study submitted to FDA to support approval of a pediatric triple ingredient OTC product [Wyeth 2004]. FDA had summarized data for the latter study as part of the basis of approval, and this summary is publicly available. The dose-independent pharmacokinetic parameters, oral clearance CL/F, half-life t½, and apparent distribution volume Vd/F from studies in children and adults are listed in Table 4.7; whereas, the doses and drug exposure parameters (AUC_{INF} and C_{MAX}) are listed in Table 4.8.

Table 4.7 Dose-Independent Pharmacokinetic Parameters (Mean, cv%) for Chlorpheniramine by Age Group

Age Group (Study Reference)	n	Age (y)	t ½ (h)	CL/F (mL/kg/min)	Vd/F (L/kg)
Adults 18 to 45 years	***167***	***----***	***20.2***	***5.0***	***7.65***
Chen 2004	18	NR	18.9 (29%)	NR	NR
Najjar 1995	13	25-45	25.5 (77%)	NR	NR
Huang 1982	5	27 to 40	31.1 (27%)	NR	NR
Koch 1998	24	18 to 40	18.5 (NR)	NR	NR
Kotzan 1982[a]	15	18 to 27	17.3 (25%)	NR	NR
Kotzan 1982[a]	15	18 to 27	14.6 (23%)	NR	NR
Vallner 1982	15	24	25.1 (33%)	NR	NR
van Toor 2001	24	20-41	17.6 (28%)	NR	NR
Wyeth 2004 (Study AR-00-02)	29	28	21.6 (30%)	5.5 (NR)	NR
Yacobi 1980	24	19 to 41	21.0 (24%)	4.40 (32%)	7.65 (27%)
Children 6 to < 12 years	***41***	***9.5***	***13.8***	***8.28***	***7.0***
Simons 1982	11	11.0 ± 3	13.1 (50%)	7.23 (44%)	7.0 (40%)
Wyeth 2004 (Study AR-00-03)	30	9.0	14.0 (28%)	8.67 (NR).	NR

a: crossover study; NR = not reported

Table 4.8 Dose-Dependent Pharmacokinetic Parameters[a] (Mean, cv%) for Chlorpheniramine by Age Group

Age Group (Study Reference)	n	Age (y)	Form - C or S	Dose (mg)	AUCINF (ng·h/mL)	AUCtau	CMAX (ng/mL)	TMAX (h)
Adults 18 to 45 years	***126***	***----***	***----***	***4***	***166.4***	***NA***	***7.37***	***3.3***
Chen 2004	18	NR	Tablet-C	4	164 (43%)	NA	7.25 (32%)	3.5 (51%)
Koch 1998	24	18 to 40	Tablet-S	4	185 (35%)	NA	7.5 (20%)	3.3 (24%)
Kotzan 1982	15	18 to 27	Liquid-S	4	65.4 (33%)	NA	5.9 (39%)	3.4 (73%)
Wyeth 2004 (Study AR-00-02)	29	28	Liquid-C	4	193.5 (39%)	NA	7.95 (16%)	3.2 (43%)
Wyeth 2002b (Study AD-99-01)	28	26	Tablet-S	4	162.5 (44%)	NA	7.27 (27%)	3.4 (45%)
Wyeth 2002b (Study AD-99-03)	12	30	Tablet-C	4	202.6 (51%)	NA	8.00 (41%)	2.9 (30%)
Children 6 to < 12 years								
Wyeth 2004 (Study AR-00-03)	30	9	Liquid-C	2	130.9 (40%)	NA	7.34 (60%)	2.9 (53%)
Adults 18 to 45 years	***96***	***----***	***----***	***8***	***248.1***	***324.6***	***13.5***	***3.0***
Huang 1982	5	27 to 40	Tablet-S	8	NR	NA	18.8 (51%)	2.7 (22%)
Kotzan 1982	15	18 to 27	Liquid-S	8	156.3 (39%)	NA	11.3 (26%)	3.8 (71%)
Najjar 1995	13	25 to 45	Tablet-S	8	431.2[b] (NR)	NA	20.5[b] (NR)	2.1 (52%)
van Toor 2001	24	20 to 41	Tablet-S	8	206.2 (32%)	NA	9.87 (21%)	NR
Vallner 1982	15	24	Tablet-S	28 x 4	NA	311.3[c] (47%)	NA	NA
Yacobi 1980	24	19 to 41	Tablet-C	28 x 4	NA	333.0[c] (44%)	NA	NA
Children 6 to < 12 years								
Simons 1982	11	11.0 ± 3	Liquid-S	4.75[d]	246.2 (51%)	NA	13.5 (26%)	2.5 (60%)

a: Except TMAX, which is not a dose-dependent parameter, but which is usually reported with CMAX.
b: geometric mean
c: AUCtau over 12 hours during which two 4-mg doses were given six hours apart, totaling an 8 mg dose over 12 hours.
d: Dose estimated from mean weight of 39.6 kg and weight-adjusted dose of 0.12 mg/kg.

Key: NA – not applicable; NR – not reported; C – combination pseudoephedrine product; S – single ingredient pseudoephedrine

Appendix 4. Safety Data from Prospective Clinical Trials in Children

APPENDIX 4

Table 5.1 Relevant AAPCC Coding Terminology: Reason for Exposure

Unintentional general	All unintentional exposures not otherwise defined. (*Most exposures of these by curious young children who gain accidental and unsupervised access are coded here)*
Therapeutic error	An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only exposures to medications or products used as medications are included. Drug interactions resulting from unintentional administration of drugs or foods which are know to interact are also included.
Unintentional misuse	Unintentional improper or incorrect use of a nonpharmaceutical substance. Unintentional misuse differs from intentional misuse in that the exposure was unplanned or not forseen by the patient.
Unintentional unknown	An exposure determined to be unintentional, but the exact reason is unknown.
Intentional misuse	An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic or euphoric effect.
Malicious	This category is used to capture patients who are victims of another person's intent to harm them
Adverse reaction	An adverse event occurring with normal, prescribed, labeled, or recommended use of the product, as opposed to overdose, misuse, or abuse. Included are cases with an unwanted effect because of an allergic, hypersensitive, or idiosyncratic response to the active ingredients, inactive ingredients, or excipients. Concomitant use of a contraindicated medication or food is excluded and is coded instead as therapeutic error.

Appendix 4

Table 5.2 Relevant AAPCC Coding Terminology: Medical Outcome Categories

No Effect	The patient did not develop any signs or symptoms as a result of the exposure
Minor Effect	The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucous membranes (e.g., self-limited gastrointestinal symptoms, drowsiness, skin irritation, first-degree dermal burn, sinus tachycardia without hypotension, and transient cough).
Moderate Effect	The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual diability or disfigurement (e.g., corneal abrasion, acid-base disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment.
Major Effect:	The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac, or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).
Death:	The patient died as a result of the exposure or as a direct complication of the exposure. Only those deaths that were probably or undoubtedly related to the exposure are coded here.
Not Followed, Judged as Nontoxic Exposure:	No follow-up calls were made to determine the outcome of the exposure because the substance implicated was nontoxic, the amount implicated was insignificant, or the route of exposure was unlikely to result in a clinical effect.
Not Followed, Minimal Clinical Effects Possible:	No follow-up calls were made to determine the patient's outcome because the exposure was likely to result in only minimal toxicity of a trivial nature (the patient was expected to experience no more than a minor effect).
Unable to follow, judged as a potentially toxic exposure:	The patient was lost to follow-up, refused follow-up, or was not followed, but the exposure was significant and may have resulted in a moderate, major or fatal outcome.
Unrelated effect:	The exposure was probably not responsible for the effect.
Confirmed Nonexposure:	This outcome option was coded to designate cases where there was a reliable and objective evidence that an exposure initially believed to have occurred actually never occurred (e.g., all missing pills are later located).

APPENDIX 4

TABLE 5.3: Maryland Poison Center (MPC) - Medical Outcomes for Calls Involving Cough and Cold Products in Children < 6 years of Age (2004)

AAPCC Medical Outcome Categories	MPC Medical Outcomes N=1078
Confirmed Non-exposure	2 (0.2%)
Unrelated Effect	9 (0.8%)
No Effect	142 (13.2%)
Not Followed, Judged as Nontoxic Exposure	161 (14.9%)
Not Followed, Minimal Effects Possible	682 (63.3%)
Minor Effect	66 (6.1%)
Moderate Effect	5 (0.5%)
Major Effect	0 (0%)
Unable to Follow, Judged as Potentially Toxic Exposure	11 (1%)
Death	0 (0%)

Appendix 4

TABLE 5.5: List of Ingredients* Searched by AAPCC's in National Poisoning and Exposure Database

Brompheniramine	Camphor	Chlophedianol
Chlorcyclizine	**Chlorpheniramine**	Codeine
Dexbrompheniramine	Dexchlorpheniramine	**Dextromethorphan**
Diphenhydramine	**Doxylamine**	Ephedrine
Guaifenesin	Loratidine	Menthol
Naphazoline	Oxymetazoline	Phenindamine
Pheniramine	**Phenylephrine**	Propylhexedrine
Pseudoephedrine	Pyrilamine	Thonzylamine
Triprolidine	Xylometazoline	

***Bold cough and cold ingredients are included in the most frequently purchased pediatric cough and cold products.

Appendix 5. Safety Data from Prospective Clinical Trials in Children

Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
Phase IV Safety and Efficacy Study of C-30 Liquid cough-cold Formula (1980) T&A10 (McNeil)	Open-label and multiple-dose design	30mL = APAP 650 mg, PSE 60 mg, CPM 4 mg, DEX 20 mg Children 6 to < 12 yr 15 mL q 4 hr Adults ≥ 12 yrs 30 mL q 4 hrs	**Population:** 109 subjects with symptoms of upper respiratory infection or allergic rhinitis accompanied by cough completed the study; 73 were adults (over 12 hr) and 36 children (over 6 but under 12 yr). (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 36 (6 <12 yr)). **Safety Results:** 21 AEs were reported in 17/36 children. 15 of the AEs were drowsiness, and 4 of those were reported as severe intensity. 44 AEs were reported in 35/73 adults. 26 of the AEs were drowsiness, and 5 of those were reported as severe intensity. In adults, there were single reports of severe intensity for dizziness, high blood sugar, nausea and high blood pressure. **Conclusions:** A rather high percentage of subjects reported AEs with drowsiness accounting for the majority of reported AEs.
Evaluation of the Efficacy and Safety of C-9-7 Cold Formula in Pediatric Patients with Symptomatology of Upper Respiratory Infection or Allergic Rhinitis (1981) T&A 13 (McNeil)	Open-label and multiple-dose design	10 mL= APAP 320 mg, PSE 30 mg, CPM 2 mg, alcohol 8.5% 10mL q 6-8 hr Up to 4 days	**Population:** 118 children with symptoms of upper respiratory infection or allergic rhinitis between 6 and 12 yrs were enrolled; 117 completed the study. (0 (0< 6 mo), 0 (6 mo<2yr), 0 (2<6 yr), and 117 (6 <12 yr)). **Safety Results:** There were no reports of deaths or serious AEs. 16/117 subjects reported AEs, of which 13/16 were tiredness. 2AEs of tiredness and 1 AE of deep sleep were rated as severe intensity **Conclusions:** 16/117 children reported AEs.
An Evaluation of the Efficacy and Safety of C-30-13 Cough-Cold	Open-label and multiple-dose design	30mL=APAP 650 mg, PSE 60 mg, CPM 4	**Population:** 100 subjects with symptoms of upper respiratory infection or allergic rhinitis accompanied by

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Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
Formula in Adult and Pediatric Patients with Symptomatology of Upper Respiratory Infection or Allergic Rhinitis (1981) T&A 15 (McNeil)		mg, DEX 30 mg, alcohol 7% Children 6 to < 12 yr 15 mL q 6 hr Adults ≥ 12 yrs 30 mL q 6 hrs Up to 4 days	cough completed the study; 50 were adults (over 12 hr) and 50 children (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 50 (6 <12 yr)). **Safety Results:** There were no reported of deaths or serious AEs. 28 AEs were reported in 24 subjects; the majority (10) reported tiredness. AEs reported were of mild or moderate intensity. **Conclusions:** The treatment was tolerated, no safety issues identified.
NDA 21-128 Multiple-dose Pharmacokinetic Study of an Ibuprofen-pseudoephedrine HCl Suspension in Children (1999) (97-024) (McNeil)	Phase I Open-label and multiple-dose design	Dose based on body weight (7.5 mg/kg IBU, 1.125 mg/kg PSE) Dosed q6h for 5 doses	**Population**: 24 healthy children enrolled (24 completed); age 4-11 yrs. (0 (0< 6mo), 0 (6mo<2yr), 4 (2<6 yr), and 20 (6 <12 yr)). **Safety Results:** There were no deaths or serious AEs reported. Overall, 25% of the subjects reported an AE. Drug related AEs reported in 3 (12.5%) of the subjects. All 3 reports were of a stomach ache. None of the subjects withdrew due to AEs **Conclusions:** The treatment was tolerated, no safety issues identified.
NDA 21-128 An Open-Label Study of the Safety of an Ibuprofen-Pseudoephedrine HCl Suspension in Children (1999) (99-086) (McNeil)	Phase III Multi-center, open-label study	Dose based on body weight (12.5 mg/kg IBU, 15 or 30 mg PSE) Dosing: every 6-8 hrs as needed; up to 4 times in 24 hrs for 3 days	**Population:** 114 children enrolled (112 completed); age 2-11 yrs with symptoms of the common cold, flu, or sinusitis. (0 (0<6mo), 0 (6mo<2yr), 66 (2<6yr), 48 (6<12yr)). **Safety Results:** There were no deaths or serious AEs reported. Overall, 18.4% of the subjects reported an AE. Drug related AEs reported in 13.2% of the subjects

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Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
			Most frequently reported AE was somnolence. 2 patients withdrew due to AEs (urticaria, stomach discomfort). **Conclusions:** The treatment was tolerated, no safety issues identified.
NDA 21-373 A Single-Dose, Randomized, Open Label, Three-Way Crossover Pharmacokinetic Study of Children's Advil Cold in 6 to <12 year Old Children AQ-99-02 (Wyeth)	Single dose, RCT, crossover PK study	IBU 100 mg +PSE 15 mg, IBU 100 mg, PSE 15 mg	**Population:** 29 healthy children (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 29 (6 <12 yr)). **Safety Results:** There was only one adverse event in the study of a subject that occurred the night before receiving PSE and therefore was unrelated to treatment. No subject discontinued due to an adverse event. No serious AEs or deaths occurred during the study. No abnormal vital signs were noted. The physical examination and laboratory evaluations results at the end of the study did not reveal any clinically significant findings. **Conclusions:** Treatments were well tolerated. There we no deaths or serious AEs reported.
NDA 21-373 Children's Advil Cold Multiple Dose Safety Study in Children 2 to < 12 Years Old AQ-99-03 (Wyeth)	Open label, uncontrolled safety study	IBU 100 mg/PSE 15 mg/5mL q 6 hrs for up to 7 days (3 days for fever)	**Population:** 106 children with symptomatic rhinitis or sinusitis (2-<12 yr). (0 (0< 6mo), 0 (6mo<2yr), 51 (2<6 yr), and 53 (6 <12 yr)). **Safety Results**: There were no deaths or serious AEs and one patient discontinued due to an AE. A total of 38 AEs were reported by 29 subjects (28%). AEs were most frequently associated with the nervous system (n=11). The most frequently reported AE was somnolence (n=7) followed by vomiting (n=3). Each of

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Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children

Citation	Study Design	Dose/Duration	Study Populations, Safety Results, Conclusions
			the following symptoms had an incidence of two: asthenia, fever, abdominal pain, nausea, tremor, and otitis media. The remaining AEs were single occurrences: back pain, common cold, headache, pain, diarrhea, dyspepsia, lymphadenopathy, lymphocytosis, hyperkinesias, nervousness, rhinitis, pruitus, rash, conjunctivitis, ear disorder, and ear pain. Of the 38 occurrences of AEs. 20 were mild, 16 were rated as moderate and two were rated as severe. The severe AEs were single occurrences of somnolence and ear pain. There were no clinically significant changes in vital signs. **Conclusions:** There were no unexpected or serious adverse events reported during the study.
NDA 21-373 A Single-Dose, Randomized, Open Label, Multicenter, Parallel Group Confirmatory Pharmacokinetic Study of Children's Advil Cold in 2 to < 6 Year Old Children AQ-00-04 (Wyeth)	Single dose, parallel, PK study	IBU 100 mg +PSE 15 mg, PSE 15 mg	**Population:** 23 children < 6 yr with acute respiratory infection. (0 (0< 6mo), 0 (6mo<2yr), 23 (2<6 yr), and 0 (6 <12 yr)). Safety Results: No serious AEs or deaths occurred during the study. No subject discontinued due to an adverse event. Three (27.3%) subjects reported three AEs (one instance each of chills, rhinitis, and otitis media) in the IBU/PSE group, while six (50%) subjects reported severe AEs (one instance each of asthenia, pain, abdominal pain, increased appetite, and rash and two instances of hypertension) in the PSE alone group. Eight of the AEs were rated as mild in severity and the remaining two (otitis media and abdominal pain) were rated as moderate. Except for rhinitis and asthenia, all the AEs were considered not to be related to study

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Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
			medication.
NDA 21-587 Children's Allergy Sinus Suspension Single-dose, three period, crossover study in Children 6 to < 12 years AR-00-03 (Wyeth)	Single dose, PK study	IBU 200 mg + PSE 30 mg + CPM 2 mg	**Population:** 32 children with allergic rhinitis. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6yr), and 32 (6 <12yr)). **Safety Results:** No deaths or serious AEs were reported in the study, and no subject discontinued treatment due to an AE**.** Nine (28.1%) subjects reported a total of 10 AEs. Somnolence and pain each occurred in 2 (6.3%) subjects. The incidence of all other AEs reported was limited to 1 subject each. **Conclusions:** There were no unexpected or serious adverse events reported during the study.
NDA 21-587 Children's Allergy Sinus Suspension Multiple-Dose Safety Study in Children 6 to < 12 Years of Age with Symptoms Consistent with Allergic Rhinitis AR-00-04 (Wyeth)	Multicenter, open label, multiple dose safety study	IBU 200 mg + PSE 30 mg + CPM 2 mg q 6 hr for 7 days	**Population:** 111 children 6 to < 12 yr suffering from upper respiratory allergies. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 111 (6 <12 yr)). **Safety Results:** There were a total of 66 AEs reported by 39 (35%) subjects. The most common adverse event in children was somnolence, 13 (12%), which in most cases resolved within two days after study drug was taken. Only two subjects reported experiencing somnolence for longer than two days after receiving the first dose of study medication. Other frequently occurring AEs included asthenia (n=9, 8%), headache (n=6, 5%), and abdominal pain, 5, 5%). Three severe AEs were judged by the investigator to be definitely, probably or possibly related to study drug: somnolence (n=1), and asthenia (n=2). **Conclusions:** AEs noted during the study were

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Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
			consistent with previously known safety profile of same combination drug in adults.
A Comparative Study of Co-administered Doses of Ibuprofen and Pseudoephedrine and Each Drug Alone in the Treatment of Primary Nocturnal Enuresis (2002) (00-131) (McNeil)	Phase II (Therapeutic Exploratory) Double blind, double dummy, placebo controlled, randomized, parallel-group, multiple-center study	(IBU/PSE, IBU/placebo, pseudo/placebo, placebo/placebo) Dose based on body weight (12.5 mg/kg IBU, 15 or 30 mg PSE) Dosed orally at bedtime for 2 weeks	**Population:** 318 children enrolled (307 completed); age 6-11 yrs. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 158 (6 <12 yr) received PSE or PSE + IBU) **Safety Results:** there were no deaths or serious AEs reported. Overall, 21.1% of the subjects reported an AE, no significant difference among treatment groups. Drug related AEs were more frequently reported with IBU/PSE (6.1%) or IBU alone (9.0%) than PSE or placebo. The most frequently reported AEs were headache, infection, abdominal pain, fever, cough increased, taste perversion. 5 subjects withdrew due to digestive system complaints. **Conclusions:** All treatments were tolerated, no safety issues identified.

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Company Sponsored, Published Literature and Post Marketing Studies

Table 2. Literature Review of Safety Data in Children

Citation	Study Design	Dose/Duration	Study Populations, Results, Conclusions
McGovern JP (1959) *Annals of Allergy* 17:915-922	Open label, non-PBO-controlled study	BRM 0.2 mg/kg/d (0<6yr) or 0.15 mg/kg/d (>6 yr) chronic dosing (3 months up to 18 months)	**Population:** 200 children with perennial allergic rhinitis. (1 (0< 6mo), 72 (6mo<2yr), 70 (2<6 yr), and 57 (6 <12 yr)). **Safety Results:** No deaths and no SAEs were reported. Only seven subjects (3.5%) reported AEs; all of them were drowsiness and of mild intensity except in one subject in the 6-12 yr age group that required discontinuation of study medication due to excessive drowsiness. No abnormal hemoglobin, WBC or differential WBC findings were observed **Conclusions:** BRM was safe and well tolerated in infants and children.
Lipschutz A (1960). *Annals of Allergy* 18:998-1003	DB, PBO-controlled trial	PSE QID x 3 days (no dosage given) alone, or PSE + Triprolidine, or PBO.	**Population:** 200 children (156 received PSE or PSE+triprolidine; estimate 100 (0<12yr) **(4 months – 17 years old*)** **Safety Results:** All subjects were administered medication without any ill effects, and no abnormal urinary or hematological findings were observed. **Conclusions:** There were no untoward effects of PSE and PSE with triprolidine in the use of these drugs
Carter, C.H. (1963) The American Journal of the Medical Sciences, 245:713-717.	DB study	A pulvule contained Novrad 50mg (l-PRX) and ASA 325mg was prepared in order to compare to DEX 30mg/ASA 325mg and to ASA 325mg	**Population:** 78 children 1-15 yrs (mean 4.1 yr) with acute UR infections (26 received DEX 0 (0< 6mo), 1 (6mo<2yr), 23 (2<6 yr), and 2 (6 <12 yr). **Safety Results:** No adverse reactions were reported by subjects for any medication. **Conclusions:** The treatments were tolerated, no safety issues identified.

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Reece, C.A. et al. American Journal of Diseases of Children, 112:124—128, 1966.	Twofold study (inpatients hospitalized for respiratory illness and a study of ambulatory patients in private practice)	Triaminicol syrup (each 5ml contains PPA 12.5mg, pheniramine maleate 6.25mg, pyrilamine maleate 6.25mg, DEX 15mg, and ammonium chloride 90mg): Dorcol pediatric cough syrup (each 5ml contains DEX7.5mg, PPA 8.75mg, GUA 37.5, and alcohol, 5%); PBO syrup	**Population**: 65 Children with the chief complaint of cough(22 children 2 mo to 9 yrs in inpatient study and 43 children 2 mo to 12 yrs in the outpatient study).* Two-thirds received DEX containing medication. **Safety Results:** No deaths or SAEs reported. **Conclusions:** No deaths or SAEs reported.
Todd G, et al. *Curr. Med. Res. Opin*. 1975;3:126-131	Two clinical trials: **Trial 1**: DB, randomized, parallel group study. **Trial 2**: DB, randomized, parallel group study.	**Trial 1**: CLEM 1 mg/b.d. increasing to 1 mg t.d.s or q.d.s. if required or CPM 4mg/b.d. increasing to 4 mg t.d.s or q.d.s. if required over the 3-week study period. **Trial 2**: CLEM elixir (0.5 mg/5ml) 1 tsp b.d. increasing by 1-2 tsp as required per physician advice or	**Population: Trial 1**: DB, 58 patients (**9.5-58** years) (28 received CPM)* **Trial 2**: 42 patients completed (**2.5-12.3 years**). (23 received CPM)* **Safety Results:** Summary of Trial 1: Side effects were minimal with both groups and drowsiness was transient with no significant difference in severity or incidence between the groups. Summary Trial 2: The CLEM group had no reports of drowsiness or tiredness; however, there was 1 incidence each of unpleasant taste, facial rash and malaise. The CPM group had 3 complaints of drowsiness and 1 patient had nausea. **Conclusions:** Side effects were minimal and drowsiness was not a problem.

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Citation	Study Design	Dose/Duration	Study Populations, Results, Conclusions
		CPM syrup (2mg/5 ml) 1 tsp b.d. increasing by 1-2 tsp as required per physician advice over a 3 week study period.	
Simons EFR, et al. *J Allergy Clin Immunol*. 1982;69(4): 376-381	Determine pharmacokinetic parameters of a single dose of CPM	single dose (0.12 mg/kg) of CPM	**Population:** 11 children (**6-16 years**) with allergic rhinitis. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 6 (6 <12 yr)). **Safety Results:** 10 children had 1 or more mild complaints of sleepiness, dry mouth, excitement, or nausea at 1 and/or 3 hours after CPM administration. The mean score of adverse effects did not differ significantly at 1, 3, 6, 9 and 30 hr from the prestudy score. **Conclusions:** The children experienced only mild transient side effects from CPM over a serum concentration range of 5.5 to 18.5 ng/mL.
Jaffe G, Grimshaw JJ (1983) Cur Med Res Opin 8(8):594-599.	Randomized, Single blind study	Actifed (triprolidine 1.25 mg + PSE 30 mg+ codeine 10 mg) or Pholeolix (APAP 150 mg, codeine 5 mg, PPA 12.5 mg)	**Population:** 217 children with cough (110 received PSE containing product). (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 110 (6 <12 yr)). **Safety Results:** There were no reports of deaths or SAEs. 54% reported drowsiness in the PSE containing group and all but one was of mild to moderate intensity. 14 subjects reported nausea (one was severe). **Conclusions:** The PSE combination product was tolerated.
Weippl G, Mauracher E (1983). *Pharmatherapeutica* 3(6):405-409.	Open, non-PBO-controlled study	Dosed 3 or 4 times daily with 2.5 or 5 ml of 'Disophrol Syrup' (1.5 mg dexbromphen-	**Population:** 30 children (**aged 5 – 12 years**) with a confirmed diagnosis of seasonal allergic rhinitis. (0 (0< 6mo), 0 (6mo<2yr), 1 (2<6 yr), and 29 (6 <12 yr). **Safety Results:** Incidence of adverse reactions was limited to one occurrence of extreme fatigue that lasted for 10 days, which did not necessitate termination of

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		iramine maleate + 30 mg PSE sulfate / 5 ml)	therapy. Vital signs were unaffected. **Conclusions:** The combination of DXBR/PSE in a syrup formulation (Disophrol) was well tolerated.
Weippl G (1984). *Clinical Therapeutics* 6(4):475-482.	Randomized, DB, comparative study	Antihistamine-decongestant-antitussive formulation (SCH 399: 0.5 mg AZA, 30 mg PSE, 10 mg DEX, t.i.d. or q.i.d., depending upon age) or with an antihistamine-expectorant formulation (DPH, AMM, SC, MTH t.i.d. or q.i.d., depending upon age) for 5 days.	**Population:** 56 children (**4 - 11 years**) presenting with symptoms of a common cold of 24 – 48 hours duration.* (29 received AZA+PSE and 26 DEX.) **Safety Results:** No adverse reactions were reported by subjects or observed by physicians. No clinically important vital signs were observed in either treatment group. **Conclusions:** The treatments were tolerated, no safety issues were identified.
Sakchainanont B, et al. Journal of the Medical Association of Thailand. 1990;73(2):96-101	DB, randomized PB)controlled study	CLEM fumarate (0.05 mg/kg/day twice a day), CPM maleate syrup (0.35 mg/kg/day, three times a day), or PBO.	**Population:** 150 patients (under 5 years of age) (48 received CPM*). **Safety Results**: There was no difference among groups with regards to slight drowsiness and sleepiness. Both antihistamine groups had not more side effects than the placebo group. **Conclusions:** The treatment was tolerated, no safety issues identified.
Hutton N, et al. (1991).	RCT	The antihistamine-decongestant drug	**Population:** 96 children, aged **6 months – 5 years** with upper respiratory symptoms consistent with a common cold.*

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Pediatric Pharmacology and Therapeutics 118(1):125-130.		(Dimetapp) contained BRP (4mg/5ml), PPA (5mg/5ml), and PE (5mg/5ml), PBO, or no medication, dosed according to the child's weight 3 times a day for 2 days.	**Safety Results:** Parents were asked if their children had any bad effects from the medicine. One child in the placebo group had loose stool, and one child in the drug group was reported to be hyperactive. A second child in the drug group was sleepier than usual. **Conclusions:** The treatment was tolerated, no safety issues identified.
Korppi M. *Acta Paediat Scand*.1991;80:969-71	DB, parallel group study	(1.5 mg/ml DEX), (1.5 mg/ml DEX and 0.2 mg/ml SAL) or PBO for 3 days. Dose was 5 ml TID for children < 7 and 10 ml TID for children > 7.	**Population:** 75 children (**1-10 years**). (49 received DEX or DEX + SAL.) **Safety Results:** Incidence of adverse events was low and equal in all groups. **Conclusions:** Incidence of adverse events was low and equal in all groups.
Taylor JA, et al. J Ped 1993;122:799-802.	RCT	1 dose at bedtime for 3 nights DEX+GUA, COD+GUA, PBO	**Population:** 141 doses in 49 pts age 18mo-12yr with nocturnal cough. **Safety Results:** Drowsiness occurred in 3 patients from the PBO group, and 3 patients from the DEX group. Diarrhea occurred in 3 patients from the PBO group and 1 patient from each the codeine and DEX groups. Hyperactive behavior was reported in 2 children receiving DEX. **Conclusions:** The study medications were tolerated. There was no safety signal.
Martinez-Gallardo F, et al.(1994). *Proceedings of the Western*	DB, PBO-controlled trial	PSE syrup (15 – 60 mg t.i.d., depending upon age), a suspension	**Population:** 65 children (**aged 2 – 16 years**) presenting with symptoms of a common cold. 30 received PSE or PSE+naproxen aged 2-12 yr (0 (0< 6mo), 0 (6mo<2yr), 6 (2<6 yr), and 24 (6 <12 yr)).

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Pharmacology Society 37:157-158.		combining PSE and naproxen (15 – 60 mg and 50 – 200 mg, respectively, t.i.d.), or PBO for 5 days	**Safety Results:** No side effects were reported. **Conclusions:** The treatment was tolerated, no safety issues identified.
Simons FE, Watson W. Journal of Pediatrics.1996; 129: 729-734. Gu X, et al. *J. Allergy Clin. Immunol.* 1996;97(1 pt. 3):199 (PK study)(abstract only)	In two sequential DB, parallel group, single dose studies	PSE, 30 or 60 mg, or PBO and 20 children received PPA, 20 or 37.5 mg or PBO.	**Population:** 41 children with allergic rhinitis (14 received PSE: (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 14 (6 <12 yr)). **Safety Results:** Both doses of both decongestants increased the pulse rate, but this was only statistically significant at 4 hr after use of the PSE 60 mg. No significant increases in blood pressure occurred after use of either decongestant. **Conclusions:** The treatment was tolerated, no safety issues identified.
Tinkelman DG. et al. Pediatric Asthma Allergy & Immunology. Vol. 10(1)(pp 9-17), 1996.	Multicenter, randomized, parallel-group study evaluated the efficacy and safety of CTZ, in a single dose or divided doses, and CPM in.	CTZ 5 – 10 mg in a single dose (n=62), CTZ 5 – 10 mg in 2 divided doses (n=61) and CPM 2 mg TID (n=63) for 2 weeks.	**Population:** 188 pediatric subjects with SAR (63 received CPM: 0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 63 (6 <12 yr)). **Safety Results:** Most of the patients who experienced AEs reported only mild-to-moderate severity. AEs were reported by 33.6% of pts in the combined CTZ groups and 38.1% of the CPM group. The majority of AEs were mild to moderate in intensity. The most commonly reported AE for CTZ was abdominal pain in 12 of 125 (9.6%) pts, compared with 3 of 63 (4.8%) pts in the CPM group. Somnolence was reported in 5 of 63 (7.9%) CPM pts and 10 of 125 (8.0%) CTZ pts in both groups. When the CTZ groups were compared, somnolence was more common in pts taking 5 mg twice daily (13%) than in those taking 10 mg daily (3.6%). Fatigue was reported by 4.0% of pts in the combined CTZ groups compared with 6.3% in the CPM group. Nausea and headache occurred in 3.2% of CTZ pts; headache occurred in 6.3% and nausea in 1.6% of CPM pts. Only one subject in the CPM group withdrew due to an adverse

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DB=double-blind **NAR**=nasal airway resistance **OL**=open label

Table 2. Literature Review of Safety Data in Children

Citation	Study Design	Dose/Duration	Study Populations, Results, Conclusions
			event. No clinically significant changes were in clinical laboratory tests were seen in this study. **Conclusions:** CTZ, given once daily or in divided doses twice daily, and CPM given 3 times daily for SAR in children aged 6-11 years was tolerated. Neither drug was associated with worsening of asthma.
Serra HA, et al. BR J Clin Pharmacol 1998;45: 147-150.	Randomized PBO controlled DB crossover	LOR (0.1 mg/kg) + PSE (1.2 mg/kg) twice daily for 2 weeks, and the other group received PBO. After a 7-day washout period, patients were shifted to the other treatment.	**Population:** 40 children (**aged 3 – 15 years**) with SAR.* (38 completed the trial and it is estimated 30 were 0<12yr.) **Safety Results:** One subject reported slight transient insomnia when receiving LOR + PSE. No changes were observed in vital signs or laboratory tests during the trial. **Conclusions:** The treatment was tolerated, no safety issues identified.
Jayaram. S. J Indian Med Assoc Vol 98 No.2, Feb 2000	Randomized DB study	Ascoril expectorant (SAL 1 mg, BRHX HCl 2 mg , GUA 50 mg, MTH 0.5 mg /5 mL) and other cough formula (DPH , AMM, SC, MTH/5 mL)	**Population:** 50 pediatric and adults patients* **Safety Results:** No serious adverse events were noted or reported in either group over the study period. **Conclusions:** The treatment was tolerated, no safety issues identified.

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Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 2. Literature Review of Safety Data in Children

Citation	Study Design	Dose/Duration	Study Populations, Results, Conclusions
Paul IM, et al. Clinical Therapeutics. 2004,Vol.26(9): 1508-1514 /Paul IM, et al. Pediatrics. 2004;114:e85-e90 Yoder KE, et al. Clin Pediatr. 2006;45:633-640	Double-blind, PBO-controlled trial.	DEX doses with children aged 2-5 years receiving 7.5 mg per dose (0.35 to <0.45 mg/kg), 6-11 receiving 15mg per dose (0.45 to <0.60 mg/kg), and children 12-18 receiving 30 mg per dose (0.60 to 0.94 mg/kg).	**Population:** 33 patients (19 girls, 14 boys), ages 2-18* with cough attributed to URI. (Estimated 22 were children 0<12yr.) **Safety Results:** The most common reported adverse event was hyperactivity (LD; 2, MD; 3, HD;1), but there was no statistically significant between-group differences in the occurrence of any adverse event. Other adverse events included insomnia, stomachache/ nausea, and dizziness. In total, there were 3 adverse events in the LD group, 4 in the MD group, and 6 in the HD group. **Conclusions:** There were no statistically significant between-group differences in the occurrence of any adverse event.
Merenstein (2006) *Arch Pediatr Adolesc Med. 160:707-712*	Randomized, DB, controlled clinical study	DPH 1 mg/kg once daily for 1 wk	**Population:** 44 children with frequent night time awakenings (22 received DPH: (0 (0< 6mo), 22 (6mo<2yr), 0 (2<6 yr), and 0 (6 <12 yr). **Safety Results:** There were no deaths and no SAEs reported. No parents reported adverse effects that caused them to stop study participation early. One patient in the DPH group acquired hand, foot, and mouth disease during the study and stopped after 5 days of intervention. Investigators and the data safety monitoring board judged that this was not related to study intervention. Two other children in the placebo group had mild adverse effects, one with hyperactivity and the other with diarrhea, and one in the DPH group also was reported as having hyperactivity. All conditions were reported by the parents to be mild. **Conclusions:** The treatment was tolerated, no safety issues identified.

*Not enough information to classify subjects into more finely divided age breaks: 0<6mo, 0<2 yr, 2<6 yr, 6<12 yr.)

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Table 3. Post Marketing Studies

Citation	Study Design	Dose/Duration	Study Populations, Safety Results, Conclusions
Porta et al. (1986) *Annals of Allergy* 340-342.	Post Marketing Surveillance from Group Health Cooperative of Puget Sound 1976 - 1983	PSE varies doses	**Population:** 100,000 filled 243,286 scripts for subjects < 65 yrs representing 3,649,290 person days at risk for hospitalization. (81,965 scripts for 0-19 yr age subset) **Safety Results:** 246 hospitalizations within 15 days of PSE all but one ruled out. One was 22 mo old female with seizure that lasted one minute. Causality was considered remote. **Conclusions:** Provides reassurance that PSE is safe as it is used in the general medical practice.
Wezorek C et al. (1995) *Clin Tox* 33(5):554 (abstract)	Prospective Study to determine Toxic Dose in Children.	PSE at doses up to > 180 mg	**Population:** 140 Children < 6 yrs who ingested PSE only (101 ingested 30-180 mg; remaining > 180 mg. **Safety Results:** Drowsiness was 21.7% in the 30-180 mg and 15.4% in the > 180 mg group. Mild hyperactivity was 6.9% in the 30-180 mg group and 15.4% in the > 180 mg group. **Conclusions:** PSE produced mild symptoms even at high doses.

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