

# The Safety and Efficacy of Cough and Cold Medicines for Use in Children

## Report for the 13 December 2007 MARC meeting

Report prepared by Sharon Sime, Medsafe, November 2007

---

### 1.0 PURPOSE

- To provide the MARC with a review of the briefing documents prepared by the FDA for their expert advisory committee's review of the safety and efficacy of cough and cold medicines available for use in children.
- To provide the MARC with a review of the ingredients approved for use in cough and cold medicines in New Zealand including their current classification, any restrictions on their use, whether or not use is recommended in children aged <2 years, and current international dosing recommendations.
- To seek the MARC's opinion as to whether the available data is adequate to determine the risk-benefit profile of cough and cold medicines used in children; and to seek the MARC's advice as to whether or not regulatory action is required for children aged <2 years and/or > 2 years of age.

### 2.0 BACKGROUND

On 15 August 2007 the FDA released a Public Health Advisory announcing that, in October 2007, the Non-prescription Drugs Advisory Committee (NDAC) would be discussing the safety and effectiveness of cough and cold medicines used in children<sup>1</sup>. This was in response to published reports of serious adverse events including death in children receiving cough and cold medicines; and a Citizen's Petition expressing concern about the safety and efficacy of cough and cold medicines used in children aged <6 years.

In January 2007, the Centre for Disease Control (CDC) published a report describing three deaths of infants aged < 6 months of age for which cough and cold medications were determined to be the underlying cause of death<sup>2</sup>. All three babies had high levels of pseudoephedrine in post-mortem blood samples. In March 2007, a Citizen's Petition provided evidence to support their request that the FDA adjust the product labelling for cough and cold medicines to state that these products have not been found to be safe or effective in children less than 6 years of age for the treatment of cough and cold; and should not be used in this age group.

In September 2007, briefing documents prepared by the FDA to inform the NDAC's decision making, were published on the FDA's website. The NDAC was asked to consider the following points:

1. The appropriateness of extrapolation of efficacy data to children based on adult PK data, and consideration of the appropriateness of age based paediatric dosing regimens.
2. The safety profile of cough and cold medicines when used in accordance with dosing instructions; and consideration of the risks associated with misuse, unintentional overdose and excessive dosing.
3. Appropriate labelling for OTC cough and cold products for use in children aged < 6 years.

---

<sup>1</sup> Public Health Advisory. Non-prescription Cough and Cold Medicine Use in Children. 15 August 2007. [http://www.fda.gov/cder/drug/advisory/cough\\_cold.htm](http://www.fda.gov/cder/drug/advisory/cough_cold.htm)

<sup>2</sup> Infant Deaths Associated with Cough and Cold Medications – Two States, 2005. MMWR Weekly 12 January 2007; 56(01); pp 1-4. [www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm)

This report will summarise the salient points from a number of these documents. However, the complete documents are also provided for the MARC's review (see references for individual reports – the full briefing document is available at [www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf](http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf)<sup>3</sup>).

## 2.1 Clinical Pharmacology<sup>4</sup>

### **Dosage advice**

In the US, paediatric dosage advice for cough and cold medicines has been determined by extrapolation from the adult dose. An expert advisory committee convened in 1976 determined that this was appropriate based on the assumption that the pathophysiology of the disease and the clinical response and pharmacologic intervention are likely to be sufficiently similar in adults and children. The following doses are recommended:

*Table 1: Paediatric dosage recommendations for cough and cold medicines*

Age of child	Fraction of adult dose
6-12 years	½ of adult dose
2 – 6 years	¼ of adult dose
<2 years	Ask a doctor

The labels for OTC cough and cold medicines indicate that a physician should be consulted for dosage advice in children aged < 2 years. Physicians must determine for themselves the appropriate doses for children under 2 years by either extrapolating adult or older children's doses or by consulting paediatric drug information handbooks (it is not clear how the dosing instructions in these handbooks were determined).

### **Pharmacokinetics**

There is very limited paediatric pharmacokinetic (PK) data available for the majority of the ingredients in cough and cold medicines. However, some data is available for pseudoephedrine and chlorpheniramine as follows:

#### Pseudoephedrine

Pseudoephedrine is completely and rapidly absorbed from the GI tract with a Tmax of 2-2.5 hours for adults and 1-2 hours for children 2-12 years. Pseudoephedrine's elimination T1/2 is 5-8 hours. Oral clearance is 26-30 L/min and appears to be higher for younger age groups.

*Table 2: Mean (CV%) pseudoephedrine pharmacokinetic parameters in healthy adults, healthy children (6-11 yrs) and paediatric allergic rhinitis patients (2-5 years)*

PK parameters	Paediatrics (2-5yr) Rhinitis patients)	Paediatrics (6-11yr) (healthy)	Adults (18-44 yr) (healthy)
Dose (mg)	15	30	60
N	7	28	24
AUC (ng.hr/ml)	1292 (41)	1735 (27)	2424 (26)
Cmax (ng/ml)	179 (17)	218 (24)	254 (21)
T ½ (h)	5(35)	4 (9)	5 (24)
CL/F (L/h)	14 (47)	19 (28)	26 (24)
CL/F (L/h*kg)	0.82	0.63	0.43

#### Chlorpheniramine

Chlorpheniramine exhibits variable and incomplete bioavailability (25-59%) and has a variable elimination T1/2. Data in the table below shows that chlorpheniramine exposure (AUC) was 32% lower in children compared to adults. In addition, clearance was greater and T1/2 was shorter compared to adults which suggests a lower exposure for chlorpheniramine in children.

<sup>3</sup> Nonprescription Drug Advisory Committee Meeting 18-19 October 2007. FDA Briefing Documents. <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf>

<sup>4</sup> Roy P. Division of Clinical Pharmacology 2. Clinical Pharmacology Review. For Dough/Cold Advisory Committee meeting Oct 18-19 2007.

Table 3: Mean (SD) chlorpheniramine pharmacokinetic parameters in healthy adults and paediatric allergic rhinitis patients (6-11 years)

PK parameters	Paediatrics (6-11yr) (healthy)	Adults (18-44 yr) (healthy)
Dose (mg)	2	4
N	30	29
Dose (mg/kg)	0.07	0.07
AUC (ng.hr/ml)	131 (52)	194 (76)
Cmax (ng/ml)	7.3 (4.4)	8(1.3)
T1/2 (h)	14 (4)	22 (6.5)
CL/F (L/h/kg)	0.52	0.33

#### Other considerations

During the first 2 years of life, physiological and biochemical processes governing drug absorption (eg gastric pH), distribution (eg quantity of body water and fat), metabolism and excretion (eg renal excretion and/or CYP-mediated hepatic elimination) undergo significant maturation. In addition, environmental factors (such as exposure to other medicines) and dietary factors (eg breast fed vs bottle fed) can affect the PK of medicines in young children. Thus extrapolating adult PK data to children may not achieve an equivalent pharmacological effect, particularly in children <2 years.

#### **Conclusions**

Paediatric dosing cannot always be obtained by simply applying weight or surface area based calculations to the adult dose. The limited PK data available for pseudoephedrine and chlorpheniramine suggests that larger doses than those currently recommended may be required to produce equivalent systemic exposure in children as in adults. Robust and well designed PK studies in children (particularly those aged <2) taking cough and cold medicines are currently lacking.

#### **2.2 Evidence for efficacy and safety from the published literature<sup>5</sup>**

The literature search identified 11 clinical trials involving the use of cough and cold medicines in children, and 7 articles reporting individual case reports or case series. Only 4 of the 11 clinical studies claimed efficacy for the product involved. There were no deaths or serious adverse effects reported in any clinical trials. Drowsiness was the most commonly reported adverse event.

A number of methodological issues were identified in the clinical studies reviewed including:

- Inadequate information provided on randomisation, blinding and power calculations. Most studies were small and were probably underpowered to show a difference between the medicine and placebo.
- Lack of placebo arm in many studies.
- The active ingredients were administered in different doses and different dosing frequencies in each study. In some studies the dose or dose frequency was probably inadequate to elicit an effect of the study drug.
- The duration of treatment varied greatly between studies - from one dose to 18 months of treatment.
- In some studies the symptoms evaluated were not related to the expected therapeutic effect of the medicine.
- Outcome measurement varied and no studies indicated whether the outcome measures had been validated. In addition, measurement of symptoms was often not undertaken at a time when the effect of the medicine would be likely to be evident.

<sup>5</sup> Lopez LA. Medical Officer's Review: Cold and Cough Products for Over-The-Counter (OTC) Use. July 24 2007.

- Symptoms of cough and cold generally improve with time and therefore it may be difficult to show a treatment effect for some of the endpoints measured.

After evaluation of the case reports and case series, the author determined that:

- Serious adverse events including death have been reported in children with infants most commonly affected. Most of these events were related to medication errors involving dosing and administration of the medicines.
- Most children who died had detectable levels of cough and cold medicines. Pseudoephedrine was reported most commonly.
- Potential confounding by underlying medical illness or interaction with other medicines could not be excluded in many of the reports.
- Death due to other causes including SIDS or child abuse cannot be excluded in most cases.

Potential reasons for the identified medication errors included:

- Parents misunderstanding or misinterpreting the recommended dose, dosing frequency or length of therapy
- Parents being unaware that they are giving a medication that contains more than once active ingredient. Hence parents unintentionally administering combination products with duplicate active ingredients.
- Using incorrect measuring device eg 1 tsp vs 1 dropper
- Parents administering a preparation intended for adults or older children
- Parents increasing the dose or giving adult preparations that may be perceived as a stronger preparation.

### **Overall Conclusions**

- Based on the review of published clinical trials in children (1½ months to 18 years old), there is no convincing evidence of efficacy of cough and cold medications when used to treat symptoms of the common cold in this population.
- The overall incidence of reported serious adverse events from these drugs is low despite their widespread use. These medications are generally safe when used appropriately and at the recommended dose and dosing frequency.
- Excessive levels of these medications in the blood from patients (from case reports) who died or had serious adverse events were mostly due to dosing and/or administration errors by caregivers.
- Although possible, paediatric clinical studies are more difficult to conduct because children are less verbal or are unable to express their symptoms well; therefore, one has to rely on the caregiver for assessment of symptoms.

## **2.3 Review of reports to the FDAs Adverse Event Reporting System (AERS) associated with the use of cough and cold medicines in children**

### *2.3.1 Reports of infant mortality associated with the use of Pseudoephedrine, phenylephrine, ephedrine, diphenhydramine, brompheniramine and chlorpheniramine<sup>6</sup>*

The AERS data base was searched for reports of fatalities in children aged <6 years of aged between 1969 and September 13 2006, associated with the use of decongestants and antihistamines.

54 fatalities associated with the use of decongestants were identified: pseudoephedrine 46; phenylephrine 4; and ephedrine 4. 43/54 cases were reported in children aged <1 year, 2 in children aged 1-2 years and 9 in children aged 2-6 years. Most deaths occurred within 5 days of initiating treatment. Overdose and/or drug toxicity were the most common adverse events reported in these cases. The reasons given for the overdose occurring included use of

---

<sup>6</sup> Akhavan-Toyserkani G, Division of Drug Risk Evaluation. Infant mortality associated with the use of cough and cold medications. 6 February 2007

multiple cough/cold products, medication errors, accidental exposures and intentional overdoses.

69 fatalities associated with the use of antihistamines were identified: diphenhydramine 33; brompheniramine 9 and chlorpheniramine 27. 41/69 cases occurred in children aged <2 years and 28 in children aged 2-6 years. Overdose and drug toxicity were commonly reported adverse events in these cases with similar reasons for overdose as identified with the decongestants.

It was concluded that the AERS cases demonstrate that the administration of cough and cold medicines in children aged <2 years could result in fatal overdoses. The factors contributing to the risk of unintentional overdoses include:

- Medication error due to lack of proper dosage guidelines may be contributing to overdose in children aged <2 years of age.
- Parents and caregivers being unaware of the risk of overdose when using multiple cough and cold medicines
- Parents may be misinformed that medicines for children aged >6 are also safe in younger children.
- Age based dosing may be inappropriate for infants who are less than average weight or were born premature.

The author recommended an educational campaign for parents and caregivers; and the addition of a statement in the product label to indicate that dosing is not recommended in these age groups due to safety concerns and lack of evidence for efficacy.

### *2.3.2 Postmarketing review of serious adverse events in children aged less than 6 years of age associated with the use of cough and cold medications<sup>7</sup>.*

The AERS database was searched for reports of serious adverse events in children aged <6 years associated with pseudoephedrine, chlorpheniramine, diphenhydramine, and dextromethorphan between 1/1/2002 and 11/5/2007. In addition, the Toxic Exposure Surveillance System (TESS) database (which is the database of the American Association of Poison Control Centres) was reviewed between 2001 and 2005 to determine the extent of poisoning in association with cough and cold medicines.

Serious adverse event (SAE) reports were identified for pseudoephedrine (150), dextromethorphan (105), diphenhydramine (83) and chlorpheniramine (63). Over 50% of SAE reports for pseudoephedrine occurred in children aged <2 years. Drug overdoses accounted for approximately 48% of the SAEs reported. Convulsions were reported more commonly in children aged 2 years and older and were more common outside of the setting of overdose. Serious cardiac and respiratory events were most commonly reported in the setting of overdoses but also occurred where the dosage did not exceed the labelled dose.

Evaluation of the TESS database identified 14 deaths in children aged < 6 years between 2001 and 2005. 8/14 deaths were due to medication errors or unintentional overdoses, 2 were due to intentional overdoses, 2 were due to adverse reactions and 2 were of unknown cause. In 9 patients sedating antihistamines were implicated in the deaths and in 7 patients pseudoephedrine or phenylephrine was implicated.

It was concluded that cough and cold medications used in children < 6 years of age have been associated with serious adverse events including death. The author's made the following recommendations:

---

<sup>7</sup> Akhavan-Toyserkani G, Chang YJ and Ahmad SR. Division of Drug Risk Evaluation. Postmarketing safety review of serious adverse events in children less than 6 years of age associated with the use of cough and cold medications. 17 September 2007

- An educational campaign for health providers and parents/caregivers to highlight the risks associated with administering these medications to children <2, and the potential for overdose to occur when using multiple cough and cold products.
- Adjust the current labelling to describe the risk of overdose occurring and to state that these products are not recommended for use in children <2.
- Consider limiting the use of cough and cold medications in children to single ingredient products only.

### 2.3.3 Review of Medication Errors involving OTC cough and cold products in paediatric patients (newborn to 5 years)<sup>8</sup>

36 cases of medication errors involving cough and cold medicines used in children aged <6 years were identified. 22 of these cases involved children aged <2 years. Of note 14 cases of medical error occurred after a parent had sought medical advice. 9 cases involved death – 7 of those were in children < 2 years. The majority of errors involved improper dosing.

It was determined that the following factors contributed to the medical errors identified: concurrent use of medicines containing the same active ingredient, or ingredients from the same therapeutic class; errors related to misinterpretation of directions for use or appropriate measuring devices; and confusion regarding products with similar names to other products with different active ingredients

It was concluded that the above data indicates that unintentional overdoses occur in children aged < 6 years using OTC cough and cold products. The following recommendations were made:

- All OTC products for children should contain a dosing device consistent with that product
- Consideration should be given to standardising the concentrations of ingredients in OTC cough and cold products.
- An overdose warning should be added to the labels
- Consideration should be given to the elimination of multi symptom products for use in children under 6 years.
- The current “ask your physician” statement on the labelling should be replaced with “Consult your physician prior to using this product”.

## 2.4 Expert opinions sought by the FDA

### 2.4.1 American Academy of Pediatrics (AAP)

The AAP considered that there is sufficient available data from paediatric studies to conclude that cough and cold medicines are ineffective in children. In addition, the AAP noted that although these medicines are generally safe when used according to the product labelling there are two situations that potentially put children at risk of serious adverse events or death when exposed to cough and cold medicines - notably:

1. Inappropriate dosing of cough and cold medicines. The AAP considers that the availability of multiple multi-ingredient preparations that may contain the same active ingredients contributes to this risk.
2. Complete lack of data to support current dosing regimens for paediatric patients. In addition, the lack of information available to physicians when the product labelling recommends consulting a physician for dosage advice. The AAP is also concerned that children under 2 appear to have a greater sensitivity to the potentially fatal effects of some of the ingredients in cough and cold medicines.

The AAP considered that extrapolation of adult efficacy data for children is not justifiable as there is available paediatric data that does not support the efficacy of these medicines. In

---

<sup>8</sup> Abate R. Postmarketing Safety Review of Medication Errors Involving Over-the-Counter Cold Products in Paediatric Patients (Newborn to Five Years). 14 September 2007

addition, there is significant age related developmental variability in both pharmacokinetics and pharmacodynamics in children such that it is clear that adults and children handle and respond to drugs differently.

The AAP expressed considerable concern at that demonstrable lack of efficacy, evidence for considerable misuse, lack of rational basis for dosing, and apparent increased sensitivity to toxicity of these preparations in children under 6 years of age. The AAP recommended that unless clear, evidence-based paediatric dosing guidelines are available for all ages, then these products should not be available for OTC use in these age groups.

#### 2.4.2 American Academy of Family Physicians (AAFP)

The AAFP considered that it is not appropriate to extrapolate adult efficacy data to children. The AAFP noted that serious complications are rare when the medications are used correctly. The AAFP supported the advice issued by the FDA to parents and caregivers in the Public Health Advisory dated 15 August 2007.

### 3.0 NEW ZEALAND EXPERIENCE & REGULATORY ACTION

#### 3.1 New Zealand status

The following active ingredients are approved for use in OTC cough and cold medicines in New Zealand. See references for the classification status of each active ingredient.

**Table 4: Dosing instructions for cough and cold medicines**

<b>Ingredient name</b>	<b>Martindale's dosage advice</b>	<b>Dosage instructions for children &lt;2 years<sup>9</sup> in NZ labelling</b>
Guaifenesin (expectorant)	Adults: 200mg-400mg Q4h Age 6-12 : 100mg-200mg Q4h Age 2-6: 50-100mg Q4h Age 6/12 – 2yrs: 25-50mg Q4h	Do not use in children aged <2. Specific advice given for other age groups.
Bromhexine (mucolytic)	Adults: 8-16mg tds	Do not use in children <2 except on medical advice. Dosage advice for children from 1 year given for some products.
Pseudoephedrine (Sympatho-mimetic decongestant)	Adults: 60mg 3-4 times per day 6-12 yrs: 30mg 3-4 times per day 2-5 yrs: 15mg 3-4 times per day	Not recommended for children aged <2 years. Specific advice given for other age groups.
Phenylephrine (Sympatho-mimetic decongestant)	Adults: Up to 20mg Q6h	Not recommended for children aged < 2 years.
Dextromethorphan (Cough suppressant)	Adults: 10-20mg Q4h 6-12 yrs: 5-10mg Q4h 2-6 yrs: 2.5-5mg Q4h	Variable labelling with respect to use in children <2 years, ranging from lack of dosage advice to specific recommendation only to use on medical advice.
Pholcodine (Opioid)	Adults: 5-10mg 3-4 times per day	No dosage advice given for

<sup>9</sup> Please note that only a selection of product labels for each active ingredient were reviewed to determine usual dosing instructions, therefore it is possible that some product labels may differ from what is indicated in Table 4.

cough suppressant)	> 5yrs: 2-5mg 3-4 times per day 1-5 yrs: 2mg tds 3/12 – 1 yr: 1mg tds but states should be avoided in children <1	children < 2 years. Specific dosage advice given for other age groups.
Doxylamine Brompheniramine Chlorpheniramine Triprolidine Promethazine (Sedating antihistamines)	Dosage advice is variable. Brompheniramine and chlorpheniramine: dosage advice is given for children aged > 6 months Triprolidine and doxylamine: dosage advice is given for adults only	Do not use in children aged less than 2 years.
Diphenhydramine (Sedating antihistamine and cough suppressant)	Diphenhydramine: dosage advice for children is 5mg/kg/day	Do not use in children aged < 2 years.

### 3.3 New Zealand regulatory action

#### 3.3.1 Reclassification of sedating antihistamines

In June 2006 the Medicines Classification Committee recommended that sedating antihistamines should be classified as prescription medicines when indicated either singly or in combination for use in children under two years of age. This was due to concerns that some sedating antihistamines had been implicated in sudden death in this age group and there were also anecdotal and published evidence of misuse and abuse of these medicines in children.

In September 2005 the New Zealand classification schedule was updated to reclassify all sedating antihistamines as follows:

- Prescription Medicines: sedating antihistamines included in preparations that are not oral dose forms.
- Restricted Medicines: products that are oral dose forms if the sedating antihistamine:
  - is the only active ingredient; or
  - is in combination with other active ingredients not including a sympathomimetic decongestant; or
  - is included in any combination pack other than a night-time dose of a day/night pack; or
  - is indicated for use in children over the age of two years.
- Pharmacy-Only Medicines: products that are oral dose forms if the sedating antihistamine:
  - is combined with one or more other therapeutically active ingredients for the treatment of coughs, colds or influenza when at least one of the other active ingredients is a sympathomimetic decongestant, and is packed and labelled only for use in adults and children two years of age and above; or
  - is included as an ingredient of the night-time dose of a day/night pack containing other therapeutically active ingredients for the treatment of coughs, colds or influenza when at least one of the other active ingredients in the pack is a sympathomimetic decongestant and is packed and labelled only for use in adults and children two years of age and above; or
  - is approved for use as a motion sickness preparation and is in a sealed container of not more than 10 tablets or capsules except when sold at a transport terminal or aboard a ship or plane.#



### 3.3.2 Phenergan – contraindication for use in children aged less than 2 years

#### November 2005

The data sheets/labelling and/or package inserts for all promethazine containing products were updated as requested in February/March 2005.

#### September 2005

Medsafe sent a follow-up letter to Sanofi-Aventis requesting that the Phenergan data sheets be updated as requested in February 2005.

#### February/March 2005

Medsafe wrote to the sponsors for all promethazine containing products to request that their data sheets, labelling and/or package inserts were updated to include the following information:

- Dosage and administration and Contraindications section - Children
  - [promethazine product name] should not be used in paediatric patients less than two years of age.”
- Warnings and Precautions - Children
  - Post-marketing cases of respiratory depression, including fatalities, have been reported with use of [promethazine product name] in paediatric patients less than two years of age.
  - Caution should be exercised when administering [promethazine product name] to children between two and twelve years old as there is the potential for central and peripheral apnoea and reduced arousal. Excessive dosages of antihistamines in children may cause hallucinations, convulsions and sudden death.
  - The use of [promethazine product name] should be avoided in children and adolescents with signs and symptoms suggestive of Reye's Syndrome.

### 3.4 Reports to CARM/WHO

See attached CARM report.

### 3.5 Reports to the National Poisons Centre

Table 5 summarises the calls received by the National Poisons Centre (from July 01 2002 to Nov 12 2007) regarding children at or below the age of 2 years who required medical observation and/or intervention. They are listed according to the dominant ingredient in cough or cold preparations sold in NZ. Preparations that contained other more toxic substances, notably paracetamol and codeine, are excluded. The Poisons Centre does not have any information on fatalities or upon the final outcome of the children following medical intervention.

Only calls where the specific age is recorded were included (over this time interval, we received a total of 6832 calls - from a total of 147188 calls received - where medical intervention was required and the age of the child was recorded at or below 2 years of age)

Table 5: (Dominant Substance Table)

Dominant Substance	Number of calls requiring medical referrals	Dominant Substance	Number of calls requiring medical referrals
bromhexine	0	Guaifenesin	0
brompheniramine	43	Phenylephrine	1
chlorpheniramine	54	pholcodine	10
Dextromethorphan	5	promethazine	28
diphenhydramine	2	pseudoephedrine	11
doxylamine	0	triprolidine	0
Overall total	154		

## 4.0 INTERNATIONAL REGULATORY ACTION

### United States (FDA)

15 August 2007

The FDA released a Public Health Advisory announcing that, in October 2007, the Nonprescription Drugs Advisory Committee would discuss the safety and effectiveness of cough and cold drug product use in children.

Consumers were informed that over-the-counter cough and cold medicines can be harmful if more than the recommended amount is used, if it is given too often, or if more than one cough and cold medicine containing the same active ingredient is used.

The following advice was offered to parents and caregivers:

- Do **not** use cough and cold products in children under 2 years of age UNLESS given specific directions to do so by a healthcare provider.
- Do not give children medicine that is packaged and made for adults. Use only products marked for use in babies, infants or children (sometimes called “pediatric” use).
- Cough and cold medicines come in many different strengths. If you are unsure about the right product for your child, ask a healthcare provider.
- If other medicines (over-the-counter or prescription) are being given to a child, the child’s healthcare provider should review and approve their combined use.
- Do not give a child medicine more often or in greater amounts than is stated on the package.
- Too much medicine may lead to serious and life-threatening side effects, particularly in children aged 2 years and younger.
- For liquid products, parents should use the measuring device (dropper, dosing cup or dosing spoon) that is packaged with each different medicine formulation and that is marked to deliver the recommended dose. A kitchen teaspoon or tablespoon is not an appropriate measuring device for giving medicines to children.
- If a measuring device is not included with the product, parents should purchase one at the pharmacy. Make sure that the dropper, dosing cup or dosing spoon has markings on it that match the dosing that is in the **directions** in the “Drug Facts” box on the package label, or is recommended by the child’s health care provider.
- If you DO NOT UNDERSTAND the instructions on the product, or how to use the dosing device (dropper, dosing cup or dosing spoon), DO NOT USE the medicine. Consult your healthcare provider if you have questions or are confused.
- Cough and cold medicines only treat the symptoms of the common cold such as runny nose, congestion, fever, aches, and irritability. They do not cure the common cold. Children get better with time.
- If a child’s condition worsens or does not improve, stop using the product and immediately take the child to a health care provider for evaluation.

12 January 2007

The Centres for Disease Control and Prevention (CDC) issued a Morbidity and Mortality Weekly Report (MMWR) article describing three deaths in U.S. infants aged less than 12 months that were associated with cough and cold medications. These medications were determined by medical examiners or coroners to be the underlying cause of death. Prescribers were advised that the cases described in this report underscore the need for clinicians to use caution when prescribing, and caregivers to use caution when administering, cough and cold medications to children aged less than 2 years.

25 April 2006:

The FDA issued a safety alert to inform healthcare professionals and caregivers that the labelling for all promethazine containing products (including syrups) had been updated to

contraindicate their use in children aged less than two years because of the potential for fatal respiratory depression.

#### 18 February 2005

The FDA informed US prescribers that Phenergan (promethazine) products were now contraindicated for use in children aged less than 2 years because of the potential for fatal respiratory depression to occur. Prescribers were advised that caution should also be exercised when administering Phenergan to paediatric patients 2 years or age and older because of the potential for fatal respiratory depression to occur. It was noted that the reports of fatal respiratory depression in association with Phenergan use were not directly related to dose.

#### **Canada (Health Canada)**

On 11 October 2007 Health Canada announced that it was in the process of determining if the labeling of cough and cold products is sufficient to ensure that parents, caregivers and prescribers have all the information needed to make an informed decision concerning the safe use of these products. Health Canada issued the following advice to consumers regarding the appropriate use of cough and cold products in children.

##### *Children under 2 years of age*

1. Do not use cough and cold products, including drugs and natural health products, in children under 2 years of age unless instructed to do so by a healthcare practitioner.
2. Even if the cough and cold products are labelled for use in children under 2 years of age (for example, they use the word "infant" in their name or have dosing instructions for infants) it is still preferable to discuss the use of these products with your healthcare practitioner before giving them to any young child.

##### *Children of all ages*

1. If it is necessary to give a cough and cold product to a child, make sure that you read all labels and instructions before doing so. If the product does not contain dose information for children, then it should not be used in children.
2. Do not give a child a larger dose than is recommended or use the product more frequently than is recommended in the labelling and instructions.
3. Take note of the medicinal ingredients in the product, particularly if you may be giving more than one product to a child. Be aware that many products contain the same medicinal ingredient(s) and combined use could lead to overdose. Some herbs used in cough and cold medications and some over-the-counter medications used to control fever may also have medicinal ingredients similar to those in other cough and cold products.
4. Because cough and cold medications often contain multiple ingredients, it is advised not to give more than one cough and cold product to a child.
5. Talk to your healthcare practitioner if you have questions about the proper use of these products, dosing and administration information, or the medicinal ingredients in the products you are using.
6. There is no cure for the common cold. Children will usually recover from coughs and colds in time on their own. The common cold is a mild, viral infection that can be managed by rest, sufficient fluid intake and comfort measures.
7. In young children and babies, it is sometimes important to rule out serious illnesses (for example, pneumonia or other infections) which may present with cold-like signs and symptoms; this is especially important if symptoms persist or if the child's condition deteriorates.
8. If you are concerned about the child's health, the child should be brought to a healthcare practitioner for medical evaluation.

## 5.0 MEDSAFE SUMMARY AND RECOMMENDATIONS

There is currently no high quality evidence that any of the ingredients approved for use in cough and cold medicines are effective in relieving the symptoms of coughs and colds in children. However, it is evident that many of the paediatric studies conducted on this issue were inadequately designed and/or underpowered to show efficacy compared to placebo. In addition, due to the subjective nature of many of the symptoms of a cold, paediatric studies may be very difficult to conduct in this area.

The safety evaluations undertaken by FDA officials including analysis of data from the FDA's AERS database, indicates that when administered according to approved dosing instructions, cough and cold medicines are generally well tolerated in children. However, as this data is obtained from spontaneous reports, it is likely to significantly underestimate the true incidence of serious adverse effects associated with these medicines. Published case reports, case series and analyses of AERS data indicate that young children, particularly those aged < 2 years, are particularly vulnerable to serious adverse effects, including death, when recommended doses of cough and cold medicines are exceeded. The deaths that have occurred have largely been the result of errors leading to inadvertent overdose of active ingredients. Analyses of post-mortem blood samples indicate that pseudoephedrine is the active ingredient most commonly implicated in these deaths.

A number of causes of error resulting in overdose have been identified including administration of more than one cough and cold medication containing the same active ingredient; administration of adult or older child formulations to infants; using an incorrect administration device eg teaspoon rather than a dropper for infant formulations; and parents misunderstanding or misinterpreting dosage instructions.

The determination of paediatric doses based on extrapolation from adult doses is unlikely to be appropriate due to differences in pharmacokinetics and pharmacodynamics in paediatric patients, particularly in children aged < 2 years. The limited available PK data suggests that current US dosing recommendations are more likely to result in inadequate plasma levels than to cause excessive levels. (Hence this may be another reason whilst paediatric efficacy studies have failed to show efficacy for any cough and cold medicines in children).

Currently in New Zealand, the labelling for most cough and cold medicines indicate that they should not be used in children < 2 years except upon medical advice. In addition, most products do not contain any dosage advice for children <2 years. Calls received by the NZ Poisons Centre indicate that cough and cold medicines containing a sedating antihistamine as the dominant ingredient were the most common calls received about children aged <2 years who required medical referrals. It is reassuring to note that sedating antihistamines are no longer available OTC for children aged <2 years in New Zealand.

Medsafe considers that there is very limited evidence for efficacy, an absence of evidence based dosage advice for the use of cough and cold medicines in children aged <2 years and evidence of significant toxicity in overdose in this age group. Therefore, Medsafe considers that the risk-benefit profile for the use of cough and cold medicines in children <2 years is currently unfavourable. However, although there is an absence of clear evidence for efficacy in children >2 years, there is some evidence that cough and cold medicines are well tolerated in this age group when administered according to current dosage recommendations. Therefore, Medsafe considers that the risk-benefit profile for the use of cough and cold medicines in children >2 years of age is currently less clear and therefore the options for regulatory action are potentially wider.

Medsafe requests that the MARC consider that available data on this issue to answer the following questions:

1. Are the available data adequate for determining the risk-benefit profile of cough and cold medicines used in any age group of children?
2. Does the MARC consider that regulatory action is warranted for children <2 and/or >2 years of age.

Potential options available to the MARC include:

1. Seeking further information and expert advice eg The Royal New Zealand College of General Practitioners, the Paediatric Society of New Zealand.
2. Regulatory action such as
  - a. contraindicating the use of all cough and cold medicines in children aged <2 years.
  - b. Recommending labelling changes such as adding a statement to the effect that “ [product name] should not be used in children under 2 years as deaths have occurred in this age group”
  - c. Recommending that the MCC consider reclassifying the active ingredients in cough and cold medicines to Prescription-Only medicines when used in children <2 years of age.
3. Await the outcome of the FDAs and Health Canada’s review of this issue before determining whether regulatory action is warranted with respect to children <2 and/or children >2 years of age.
4. Issuing consumer advice in line with the following advice issued by Health Canada:
  - *If it is necessary to give a cough and cold product to a child, make sure that you read all labels and instructions before doing so. If the product does not contain dose information for children, then it should not be used in children.*
  - *Do not give a child a larger dose than is recommended or use the product more frequently than is recommended in the labelling and instructions.*
  - *Take note of the medicinal ingredients in the product, particularly if you may be giving more than one product to a child. Be aware that many products contain the same medicinal ingredient(s) and combined use could lead to overdose. Some herbs used in cough and cold medications and some over-the-counter medications used to control fever may also have medicinal ingredients similar to those in other cough and cold products.*
  - *Because cough and cold medications often contain multiple ingredients, it is advised not to give more than one cough and cold product to a child.*
  - *Talk to your healthcare practitioner if you have questions about the proper use of these products, dosing and administration information, or the medicinal ingredients in the products you are using.*
  - *There is no cure for the common cold. Children will usually recover from coughs and colds in time on their own. The common cold is a mild, viral infection that can be managed by rest, sufficient fluid intake and comfort measures.*
  - *In young children and babies, it is sometimes important to rule out serious illnesses (for example, pneumonia or other infections) which may present with cold-like signs and symptoms; this is especially important if symptoms persist or if the child’s condition deteriorates.*
  - *If you are concerned about the child’s health, the child should be brought to a healthcare practitioner for medical evaluation.*

## 6.0 REFERENCES (Enclosed for your review)

NZPhvC report re use of cough and cold medicines in children.

FDA Briefing information:

- Schiffenbauer J. Executive Summary to FDA briefing information.
- Roy P. Division of Clinical Pharmacology 2. Clinical Pharmacology Review. For Cough/Cold Advisory Committee meeting Oct 18-19 2007.
- Lopez LA. Medical Officer's Review: Cold and Cough Products for Over-The-Counter (OTC) Use. July 24 2007.
- Akhavan-Toyserkani G, Chang YJ and Ahmad SR. Division of Drug Risk Evaluation. Postmarketing safety review of serious adverse events in children less than 6 years of age associated with the use of cough and cold medications. 17 September 2007
- Akhavan-Toyserkani G, Division of Drug Risk Evaluation. Infant mortality associated with the use of cough and cold medications. 6 February 2007
- Abate R. Postmarketing Safety Review of Medication Errors Involving Over-the-Counter Cold Products in Paediatric Patients (Newborn to Five Years). 14 September 2007

Other references

- FDA Public Health Advisory. Non-prescription Cough and Cold Medicine Use in Children. 15 August 2007. [http://www.fda.gov/cder/drug/advisory/cough\\_cold.htm](http://www.fda.gov/cder/drug/advisory/cough_cold.htm)
- Health Canada Advisory. Recommendations for the Appropriate Use of Cough and Cold Products in Children. 11 October 2007. [http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007\\_147\\_e.html](http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_147_e.html)
- Classification status of the active ingredients approved for use in cough and cold medicines in New Zealand.
- Review of the classification definitions for controlled drugs in New Zealand