

## **Submission for the reclassification of dextromethorphan, guaifenisin, ipecacuanha and phenylephrine to a pharmacy based classification as recommended by the Cough Cold Review Group.**

**This submission was prepared by Andi Shirtcliffe on behalf of Integrated Pharmacy Care Ltd, as contracted by Medsafe New Zealand.**

The Medicines Adverse Reactions Committee (MARC) and the Cough and Cold Review Group (CCRG) have advised that the balance of risks and benefits for cough and cold medicines in children under six years of age is unfavourable and has made recommendations to improve the safety profile of these medicines. These concerns relate to:

- a lack of evidence of efficacy of the chemical entities listed below in children for the treatment of the symptoms of the common cold and
- evidence of harm of the chemical entities listed below in children.

Cough and cold medicines have been used for many years and it has been noted that there may be a public perception of safety and efficacy of these medicines. The reporting rate for serious adverse reactions involving cough and cold medicines in children in New Zealand is very low. However, this is not surprising as many of the adverse reactions are similar to symptoms of the common cough and cold and the reporting rate for all over the counter medicines is very low. Given the lack of evidence of efficacy and the nature of the condition (i.e. self limiting) it should be considered whether any risk is acceptable in the patient population involved.

### General

Cough cold remedies have been widely available in the over the counter arena for many years now, and there is wide acceptance of use of these products in the paediatric population. However, the dosing guidance for these products in this population has a spurious history and is not based on 'good science'. The fact that these medications are widely marketed and used despite the lack of evidence of efficacy can be explained in part by their regulatory history.

This class of drugs was first marketed well before 1972, the year that the FDA began a comprehensive review of hundreds of over the counter cough and cold preparations. The FDA obtained input from an expert advisory panel, solicited public comment on proposed rules, and prepared a monograph outlining conditions of use. In 1976, the advisory panel endorsed the use of some over the counter ingredients for cough or cold symptoms in adults but, in the face of negligible or nonexistent data on paediatric use, recommended against their marketing for children under two. For older children, it endorsed the extrapolation of doses from those recommended for adults, using a crude formula: half the adult dose for children between six and eleven years of age and a

quarter of the adult dose for children between two and five years. Dose recommendations were calculated for children as young as six years for antihistamines and as young as two years for all other categories of cough or cold drugs. The FDA adopted these guidelines in its monograph but permitted manufacturers to market the drugs for children below these ages if labelling instructed parents to consult a doctor before use. In the ensuing thirty years, the FDA never returned to review the effects of these preparations in young children.

In short it has been accepted that these medicines are safe for use in children based on little or no evidence and no robust review of the available data. This review has now been undertaken and it has been identified that there are appreciable risks associated with their use in paediatric populations, coupled with a lack of evidence of efficacy.

In some instances medicines are in fact used in paediatric populations when there is little evidence for their use e.g. palliative care. However in these instances the medicines are not 'generally' available to the paediatric population. Rather a decision is made on a case by case basis, with health professional involvement in the decision making process to determine the balance of risks and benefits. This is not the case with the current classification for the cough cold medicines being considered here. At this stage there appears to be insufficient safety data to contraindicate the use of these entities in children above the age of six years. However the principles of medicine use in children still apply and case by case decisions should be made with the potential input of either trained staff or a health professional. This would be achieved by moving the classification of these entities to a pharmacy based classification. In a pharmacy there is much more likelihood of parents or caregivers receiving instruction on how to use these medicines, thus decreasing the likelihood of misuse or overdose.

These products all currently have a pharmacy based classification in the United Kingdom, and it would be preferable for New Zealand to demonstrate consistency. Although at this stage it is not known what direction will be taken in Australia, the patterns of medicine use are not dissimilar to the United Kingdom. New Zealand would certainly wish to demonstrate consistency with the Australian market at least due to the agreement to harmonise their respective classification schedules and from a practical perspective for the pharmaceutical sector (e.g. ease of labelling, packaging).

The cough cold product range is a complicated one with a multitude of products, strengths and both single ingredient and multiple ingredient products are available. This causes considerable confusion for patients and their caregivers when attempting to choose the most suitable product. Although it is not compulsory for pharmacist or staff intervention to occur with all pharmacy based products, this particular product category does in practice result in more input from pharmacy staff largely because of the complexity of the product range. This results in more informed decision making around product selection and potentially safer medicine utilisation.

In addition to these general considerations, the potential for abuse with dextromethorphan is in itself a compelling argument for restricting the sale and supply medicines containing this ingredient. Pharmacy staff members are experienced in intervening and handling

cases of over the counter medicine misuse and abuse. The mere restriction of supply to pharmacy retail outlets will act as a disincentive to drug seekers as they are less numerous than supermarkets, and the personal attention that customers receive in pharmacies will act as a deterrent.

Although at this stage there is insufficient evidence to restrict access to phenylephrine based on potential for abuse there are sufficient safety concerns around adverse drug reactions to warrant restricting the supply to a venue where advice is possible and likely to occur.

The first line recommended therapy for the common cold is for supportive measures e.g. rest and fluids. When cough cold remedies are freely available in supermarkets this is sending a message to the population that they are 'safe' and hence can (and should?) be used. If the adult formulations of these products remain available at general sale there is a risk that members of the public will extrapolate this concept to children e.g. by estimating a child's dose based on the adult dose on the packaging. Moving these products to a pharmacy based classification is one significant step in changing public perception and behaviour around use of over the counter medicine use in children.

In conclusion, changing the classification of dextromethorphan, guaifenesin, ipecacuanha and phenylephrine to a pharmacy based classification as recommended by the Cough Cold Working Party will:

- Decrease exposure of children over the age of six years to medicines that have little evidence of benefit and documented evidence of harm.
- Reduce the risk of unsafe extrapolation of adult dosages to children and the risk of overdose that this brings with it.
- Result in safer use of these medicines if the proposed warning statements and packaging changes are actioned.
- Maximize the chances of 'case by case' decision making with respect to cough and cold medicine use.
- Result in increased access to written information about use of medicines in general and cough/cold medicines in particular.
- Increase differential diagnosis awareness and relevant action/referral.
- Increase the likelihood of patients and their caregivers receiving instruction on safe use of these medicines.
- Result in a more consistent classification scheduling with the United Kingdom and potentially Australia.
- Ensure that cough/cold medicines with more evidence of harm and less evidence of benefit are classified consistently with other potentially less harmful cough/cold medicines (see page eleven).
- Result in more informed decision making around cough/cold medicine use due to the complexity of the product ranges available.
- Decrease the potential for abuse, in particular with respect to dextromethorphan.
- Send a significant signal to the market place that behaviour around use of over the counter cough cold medicines in children of all ages needs to change.

**PART A**

**1 International Non-proprietary Name**

	<b>International Non-proprietary name</b>
dextromethorphan	dextromethorphan
guaiphenesin	guaifenesin
ipecacuanha	ipecacuanha
phenylephrine	phenylephrine

**2 Proprietary name(s)**

<b>Brand name</b>	<b>Ingredients intended to treat cold symptoms</b>
Actifed CC Chesty Cough	guaifenesin
Amcal Expectorant Syrup	guaifenesin
Baxters Lung Preserver	ipecacuanha
Bendryl Dry Forte	dextromethorphan
Benylin Chesty Cough	guaifenesin
Broncelix Expectorant	guaifenesin
Brondecon Expectorant	guaifenesin
Buckleys DM	dextromethorphan
Cepacol Cough, Lemon	dextromethorphan
Codral Cold & Flu	phenylephrine
Coldrex Hot Remedy Cold & Flu Plus with Nasal Decongestant	phenylephrine
Coldrex PE Cough, Cold & Flu	phenylephrine & guaifenesin
Coldrex PE Sinus	phenylephrine
Dexi-Tuss Cough Linctus Junior Dry	dextromethorphan
Dexi-Tuss Cough Liquid Dry	dextromethorphan
Dextromethorphan Cough Mixture	dextromethorphan
Dimetapp Chest Congestion Drops	guaifenesin
Dry Cough Mixture	dextromethorphan
Dry Irritating Cough Mixture	dextromethorphan
Lemsip Chesty Cough Mixture	guaifenesin
Lemsip Max All-In-One Cold & Flu	phenylephrine & guaifenesin
Lemsip Max Cold & Flu Day & Night	phenylephrine
Lemsip Max Cold & Flu Daytime	phenylephrine

<b>Brand name</b>	<b>Ingredients intended to treat cold symptoms</b>
Lemsip Max Cold & Flu Direct Blackcurrant)	phenylephrine
Lemsip Max Cold & Flu Direct (Lemon)	phenylephrine
Lemsip Max Cold & Flu Goodnight	phenylephrine & guaifenesin
Lemsip Max Cold & Flu with Decongestant	phenylephrine
Lemsip Max Cold & Flu with Decongestant Hot Drink	phenylephrine
Lemsip Max Flexi Cold & Flu	phenylephrine
Lemsip Max Sinus	phenylephrine
Maxiclear Cold and Flu Relief	phenylephrine
Maxiclear Hayfever and Sinus Relief	phenylephrine
Maxiclear Sinus and Pain Relief	phenylephrine
Maxiclear Sinus Relief	phenylephrine
Medco Tickly Cough Mixture	dextromethorphan
No Frills Cough Mixture	ipecacuanha
Nurofen Cold & Flu PE	phenylephrine
Panadol Cold & Flu Max + Decongestant Powder	phenylephrine
Panadol Cold & Flu Max + Decongestant Tablets	phenylephrine
Panadol Cold & Flu Relief PE	phenylephrine & dextromethorphan
Panadol Sinus Relief PE	phenylephrine
Robitussin Chesty Cough	guaifenesin
Robitussin Cough & Chest Congestion	guaifenesin & dextromethorphan
Robitussin Dry Cough	dextromethorphan
Robitussin Dry Cough Forte	dextromethorphan
Robitussin EX Cough Syrup	guaifenesin
Robitussin Paediatric Chesty Cough	guaifenesin
Sinutab PE Sinus & Pain Relief	phenylephrine
Strepsils Chesty Cough Syrup	guaifenesin
Strepsils Dry Cough	dextromethorphan
Strepsils Dry Cough Extra Strength	dextromethorphan
Strepsils Dry Cough Syrup	dextromethorphan
Sudafed PE Nasal Decongestant	phenylephrine
Sudafed PE Sinus + Pain Relief	phenylephrine
Vicks Cough Syrup Honey Flavour for Dry Cough	dextromethorphan
Vicks Cough Lozenges Honey Flavour for Dry Cough	dextromethorphan
Vicks Cough Syrup Honey Flavour for Chesty Cough	guaifenesin
Vicks Formula 44 Expectorant & Cough Suppressant Syrup	dextromethorphan & guaifenesin
Vicks Formula 44 for Dry Coughs	dextromethorphan
Vicks Formula 44 for Chesty Coughs	guaifenesin

**3 Name of company/organisation/individual requesting reclassification:**

Medsafe

**4 & 5 Dose form(s) and strength(s) for which a change is sought/Pack size and other qualifications:<sup>1</sup>**

dextromethorphan	in liquid form containing 0.25% or less or in solid dose form containing 15 milligrams or less per dose form when in packs containing not more than 600 milligrams and with a recommended daily dose of not more than 120 milligrams	General Sale
guaiphenesin	for oral use in medicines containing 2% or less or 200 milligrams or less per dose form; for oral use in modified release form with a maximum recommended daily dose of not more than 2.4 grams sold in a pack containing not more than 5 days supply approved by the Minister or the Director-General for distribution as a general sale medicine	General Sale
ipecacuanha	in medicines containing 0.2% or less of emetine	General Sale
phenylephrine	for nasal or ophthalmic use in medicines containing 1% or less; for oral use in medicines containing 50 milligrams or less per recommended daily dose and in packs containing 250 milligrams or less of phenylephrine per pack.	General Sale

**6 Indications for which change is sought:**

The change of classification is sought for the treatment of the symptoms of cough and cold.

**7 Present classification of medicines:**

General Sales Listing

**8 Classification sought:**

A pharmacy based classification i.e. Pharmacy Only Medicine or Restricted (Pharmacist) Medicine.

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<sup>1</sup> <http://www.medsafe.govt.nz> <accessed December 2009>

**9 Classification status in other countries (especially Australia, UK, USA, Canada).**

The steps up to and the actions taken by major regulatory authorities worldwide are summarised in the following table.

<b>Date</b>	<b>Organisation</b>	<b>Warning/Advice</b>	<b>Regulatory Action</b>
<b>United States</b>			
Jan 2006	American College of Chest Physicians	Question use of cough medicines in children.	None taken. In the USA most OTC cough and cold medicines are marketed under the authority of a monograph. Amendment of the monograph can take many years to implement. Most companies in the US have voluntarily amended product labels to state 'do not use in children under four years of age' or words to that effect.
March 2007	Citizen's Petition submitted to FDA	Concerned regarding safety and efficacy of non-prescription cough and cold medicines in children less than six years of age.	
Aug 2007	FDA Advisory	Do not use cough and cold products in children under two years unless given specific directions to do so by a healthcare provider.	
Jan 2008	FDA Advisory	Cough and cold medicines not be used to treat infants and children less than two years because serious and potentially life-threatening side effects can occur from such use.	
<b>Canada</b>			
Oct 2007	Health Canada Advisory	Do not use in children under two years.	Voluntary recall of products by sponsors.
Dec 2008	Health Canada Advisory	Use contraindicated in children less than six years of age.	Products required to be re-labelled by Autumn 2009.
<b>United Kingdom</b>			
March 2008	MHRA	Recommended that cough and cold preparations should not be used in children under two years of age.	Relabelled by Oct 2008 with products labelled for use in less than two years removed from general sale.
Feb 2009	MHRA	Recommended that cough and cold medicines should not be used in children under six years and restricted the sale of products for six to twelve year olds to pharmacy only.	No product recall, packaging expected to be updated for Autumn/ Winter 2009.
<b>Australia</b>			
April 2008	TGA	Contraindicated the use of cough and cold medicines in children under two years.	To be implemented by June 2009. Recall of non-compliant stock not required.

**10 Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute.**

Sales volumes and dates of consent to distribute information were not available at the time of writing. Toxicology/adverse drug reaction reporting does not provide a denominator and there is significant underreporting on over the counter medicines in any case, therefore this information does not give an indication of market size. The fact that the market is large enough to support such a wide range of products gives an indication that the market size is large.

The following reference may give some useful indication.

*One US study from 1994, relying on interview data from the Longitudinal Follow-up to the National Maternal and Infant Health Survey, found that approximately one third of three year old children had used an OTC cough cold medicine within the previous thirty days, and a 2007 study from England based on mail survey data from the Avon Longitudinal Study of Parents and Children identified use of cough cold medicines in the previous year by two thirds of children three to four and a half years of age and by approximately half of children five and a half to seven and a half years of age. A national telephone survey conducted in November 2007 reported that fifty six percent of parents of children who were younger than two and seventy nine percent of parents of children who were aged two and six years had ever given their children a cough cold medicine, but no additional information on types of products or patterns of use was collected.<sup>2</sup>*

**11 Labelling or draft labelling for the proposed new presentation(s)**

**12 Proposed warning statements if applicable.**

No draft labelling was available at the time of writing this submission.

Proposed warning statements and packaging changes required as part of the section 36 notice already issued to companies distributing medicines intended to treat the symptoms of coughs and colds:

- ‘Must not be used in children under six years of age’, or equivalent.
- Amend the package labelling to ensure that there are no dosage instructions for children less than six years of age.
- If the product has a data sheet and/or consumer medicine information to add to the contraindications section that it is contraindicated in children less than six years of age and remove dosage instructions for children under six years of age.

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<sup>2</sup> Vernacchio L, Kelly J.P., Kaufman D.W., Mitchell A.A., Cough and Cold Medication Use by US Children, 1999 2006: Results From the Slone Survey. Pediatrics 2008; 122:e323-e329



- If the product has a package insert, include ‘Must not be used in children under six years of age’, or equivalent wording, and remove any dosage instructions for children under six years of age.
- Amend the package labelling to include a maximum daily dose.
- Propose improvements to the dosing instructions.
- Amend the package labelling to state that it should not be taken with any other medicine (including complementary medicines) intended to treat the symptoms of the common cold without healthcare professional advice.
- Amend the package labelling to inform parents/guardians to seek advice from a healthcare professional before using in children aged six years and over.
- Amend the package labelling, data sheet, CMI and package insert to include sedation as an adverse reaction where appropriate.
- Prepare and submit consumer medicine information for publication on the Medsafe website.
- Supply an accurate measuring device with the medicine.
- Supply the medicine in child resistant packaging.

**13 Other products containing the same active ingredient(s) and which would be affected by the proposed change.**

See section Part A(2).

## **Part B**

### **1 A statement of the benefits to both the consumer and to the public expected from the proposed change.**

Enhanced safety around the supply and sale of these medicines is the main benefit to the consumer and to the public. When these medicines are provided from a pharmacy there are the following benefits:

- There is a legislative requirement for there to always be a registered pharmacist present. This does not necessarily mean that a pharmacist would be involved in all sales (although this would be the case in the event that any of these medicines are reclassified to restricted (pharmacist) medicine). However, it does mean that it is always possible to access the informed guidance and advice of an appropriately qualified health professional. Pharmacists have extensive experience at recognising red flag warning signs in the over the counter triage situation and referring patients on to general practice or emergency departments where required.
- In the event that a pharmacist is not involved in the sale, there is a good chance that a pharmacy assistant who has received some training in OTC medicines provision (if not specifically cough/cold medicines) would be involved in the sale. Or indeed a pharmacy technician, who would certainly have received adequate training. It is acknowledged that not all pharmacy assistants have this training consistently across the country. However, the opportunity for such training is non-existent in the current supermarket retail environment, so such advice does not occur at all with the current classification.
- Pharmacies around the country also tend to have written advice that can be taken away by the consumer. In particular the Pharmaceutical Society's Self Care Card range has a Cough/Cold consumer fact card.

### **2 Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated**

By definition the common cold is an acute self-limited illness involving the upper respiratory tract that is caused by a virus.

The clinical manifestations of colds are largely subjective, often with little in the way of objective findings in older children and adults. Sore/scratchy throat, nasal obstruction, moderate rhinorrhea, and malaise may be experienced by the person with the cold but may not be apparent to others. When present, cough, sneezing or hoarseness will be notable. Moderate anterior cervical adenopathy is common in children with colds. With few exceptions, the clinical manifestations of the cold are similar regardless of the specific virus causing the illness.

The natural history of a cold in infants or preschool age children is different from that in adults. First, fever is very uncommon in an adult with a cold but is common during the first three days of a cold in preschoolers. Second, nasal congestion and sore throat

associated with colds are readily appreciated by an adult, but similar symptoms in the preschool child typically go unreported. Instead, the parent and/or physician may notice nasal involvement only when coloured nasal secretions appear. A cold in an adult usually lasts for less than a week, whereas an uncomplicated cold in a young child usually persists for ten to fourteen days.

Sinuses, ear drainage passages and bronchial tubes are small in children and easily obstructed by mucus and mucosal swelling. In young children the adenoids and tonsils are relatively larger than in adults. Swelling of the adenoids and tonsils is therefore more likely to cause obstruction in children. Children tend to swallow phlegm rather than coughing it out like adults. Sometimes this causes them to vomit up the swallowed phlegm. The common cold can lead to secondary infections which require medical attention in both adults and children.

In short the common cold lends itself to self diagnosis or to diagnosis by a pharmacist, pharmacy technician or pharmacy assistant. Some side effects of these medicines are similar in presentation to the symptoms of a common cold so public safety would be enhanced if these medicines were only made available where input from adequately trained staff is possible to enable/enhance differentiation between these two phenomena.

As can also be seen above, the presentation of the common cold in children is different from the presentation of common cold in adults. It is beneficial for the supply of cough cold remedies and advice around the common cold to be from a pharmacy where access to informed advice is possible to minimize the chance of misdiagnosis.

### **3 Relevant comparative data for like compounds**

Bromhexine and topical decongestants are medicines that are currently used for the symptomatic relief of the common cold (amongst other indications) and are also currently restricted to pharmacy based classifications. The safety and efficacy of these agents were independently reviewed by Dr Ruth Savage and Dr Linda Bryant on behalf of the Cough Cold working party, and their power point summaries are appended at the end of this submission. Dr Savage is a member of the Medicines Adverse Reaction Committee (MARC) and works at the Centre for Adverse Reactions Monitoring (CARM). Dr Bryant is a clinical advisory pharmacist member of the MARC.

**Safety:** Dr Savage concluded that there appears to be fewer serious and fatal reactions to topical nasal decongestants and even more so, mucolytics than other cough and cold preparations.

**Efficacy:** Dr Bryant concluded that for mucolytics and topical decongestions, there was inadequate evidence of benefit in children less than twelve years old from good randomised trials in children with common cold /cough.

These agents currently have a pharmacy based classification, and independent assessments of available safety and efficacy data appear to support these classifications. Therefore it would seem logical to move other medicines for the symptomatic treatment

of the common cold/cough which also have little evidence of benefit but more evidence of harm to pharmacy based classifications.

#### **4 Local data or special considerations relating to New Zealand**

Local safety data is covered in Dr Savage's presentations. There does not appear to be any significant local clinical trial/efficacy data in this area. In addition to this there are no obvious special considerations relating to New Zealand although the following points should be noted:

- Geographically community pharmacy covers New Zealand reasonably comprehensively which ensures reasonable access to adequately trained healthcare professionals and their staff for the majority of the New Zealand public.
- New Zealand has a Restricted (Pharmacist) medicine category which is a useful category for when direct involvement of a healthcare professional is regarded as necessary for public safety.
- Legislation requires a pharmacist to be present at all times in a pharmacy therefore a pharmacist is always reasonably accessible for the public to consult.

## 5 Interactions with other medicines

	<b>Interactions</b>
Dextromethorphan	<p>Severe and sometimes fatal reactions have been reported after use of dextromethorphan in patients receiving MAOIs. Dextromethorphan is primarily metabolised by the cytochrome P450 isoenzyme CYP2D6; the possibility of interactions with inhibitors of this enzyme, including amiodarone, haloperidol, propafenone, quinidine, SSRIs, and thioridazine, should be borne in mind.</p> <p>Antiarrhythmics: Quinidine can increase serum concentrations of dextromethorphan markedly, and some patients have experienced symptoms of dextromethorphan toxicity when the two drugs have been used together<sup>3,4</sup> Based on this interaction, the combination has been studied for its therapeutic effect in amyotrophic lateral sclerosis. Amiodarone also appears to be able to increase serum concentrations of dextromethorphan.<sup>5</sup></p> <p>Antibacterials: Serotonin syndrome-like symptoms have occurred when dextromethorphan has been taken with linezolid.</p> <p>Antidepressants: A patient receiving fluoxetine experienced visual hallucinations after she began taking dextromethorphan.<sup>6</sup> The hallucinations were similar to those she had had 12 years earlier with lysergide. She had previously taken dextromethorphan alone without any adverse reactions. A serotonin syndrome has been reported in a patient who took a cold-remedy containing dextromethorphan while receiving paroxetine.<sup>7</sup></p>
Guaifenesin	None noted in Micromedix or Stockley's Drug Interactions. A search on PubMed (using 'guaifenesin' and 'drug interactions') did not produce any drug interactions for guaifenesin.
Ipecacuanha	<p>The action of ipecacuanha may be delayed or diminished if it is given with or after charcoal; antiemetics may also reduce its effect.</p> <p>Food: Milk had been believed to impair the emetic efficacy of ipecacuanha but there was no significant difference in the time to onset of vomiting, the duration of vomiting, or the number of episodes in 250 children who were given ipecacuanha syrup with milk compared with 250 given ipecacuanha syrup with clear fluids.<sup>8</sup></p>

<sup>3</sup> Zhang Y, et al. Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. Clin Pharmacol Ther 1992; 51: 647-55. (PubMed id:1611804)

<sup>4</sup> Pope LE, et al. Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. J Clin Pharmacol 2004; 44: 1132-42. (PubMed id:15342614)

<sup>5</sup> Funck-Brentano C, et al. Influence of amiodarone on genetically determined drug metabolism in humans. Clin Pharmacol Ther 1991; 50: 259-66. (PubMed id:1914360)

<sup>6</sup> Achamallah NS. Visual hallucinations after combining fluoxetine and dextromethorphan. Am J Psychiatry 1992; 149: 1406. (PubMed id:1530079)

<sup>7</sup> . Skop BP, et al. The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. Am J Emerg Med 1994; 12: 642-4. (PubMed id:7945606)

<sup>8</sup> . Klein-Schwartz W, et al. The effect of milk on ipecac-induced emesis. J Toxicol Clin Toxicol 1991; 29: 505-11. (PubMed id:1684208)

	<b>Interactions</b>
Phenylephrine	<p>As for other sympathomimetics phenylephrine has mainly direct alpha-agonist properties and is less liable than adrenaline or noradrenaline to induce ventricular fibrillation if used as a pressor agent during anaesthesia with inhalational anaesthetics such as cyclopropane and halothane; nevertheless, caution is necessary. Since phenylephrine is absorbed through the mucosa, interactions may also follow topical application, particularly in patients receiving an MAOI (including a RIMA).</p> <p>Cardiovascular drugs: Hypertensive reactions have been reported in a patient stabilised on debrisoquine when given phenylephrine orally,<sup>9</sup> in patients receiving reserpine or guanethidine when given phenylephrine eye drops,<sup>10</sup> and a fatal reaction occurred in a patient receiving propranolol and hydrochlorothiazide also after the instillation of phenylephrine eye drops.<sup>11</sup></p>

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<sup>9</sup> Aminu J, et al. Interaction between debrisoquine and phenylephrine. Lancet 1970; ii: 935-6. (PubMed id:4097321)

<sup>10</sup> . Kim JM, et al. Hypertensive reactions to phenylephrine eyedrops in patients with sympathetic denervation. Am J Ophthalmol 1978; 85: 862-8. (PubMed id:677215)

<sup>11</sup> Cass E, et al. Hazards of phenylephrine topical medication in persons taking propranolol. Can Med Assoc J 1979; 120: 1261-2. (PubMed id:221086)

## 6 Contraindications

Dextromethorphan is contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to dextromethorphan.<sup>12</sup>

Guaifenesin is contraindicated in patients who have a known hypersensitivity to guaifenesin. Caution is advised during lactation, pregnancy. Warnings/precautions include not for persistent cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema or cough accompanied by excessive secretions. When used for self-medication (OTC), contact healthcare provider if needed for more than seven days or for a cough with a fever, rash, or persistent headache.<sup>13</sup>

Ipecacuanha is contraindicated in patients with a known hypersensitivity to ipecacuanha; unconscious patients; patients with no gag reflex; following ingestion of strong bases, acids, or volatile oils; when seizures are likely. Warnings/Precautions include: do not confuse ipecac syrup with ipecac fluid extract, which is fourteen times more potent; use with caution in patients with cardiovascular disease and bulimics; may not be effective in antiemetic overdose.<sup>13</sup>

Phenylephrine is contraindicated in patients with known hypersensitivity to phenylephrine; who have taken in the last two weeks a monoamine oxidase inhibitor (MAOI); with severe hypertension or coronary artery disease; with narrow-angle glaucoma; with stenosing peptic ulcer; with symptomatic prostatic hypertrophy; with bladder neck obstruction; with pyloroduodenal obstruction; under six years of age; who are lactating; who are pregnant; severe hyperthyroidism.<sup>14,15</sup>

## 7 Possible resistance

Not applicable.

## 8 Adverse events – nature, frequency etc.

The following information is based on a presentation provided to the Cough Cold Working Party by Dr Ruth Savage. This presentation considered the severity (rather than seriousness) of the adverse effects and the likelihood of harm. This presentation was prepared based on a literature evaluation looking at data in children and Pharmacovigilance data pertinent to children. Appendix II contains information from Micromedix providing adverse event information in the general population.

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<sup>12</sup> <http://www.tga.gov.au/npmuds/pi-dextromethorphan.rtf> updated 2005 <accessed 21 December 2009>

<sup>13</sup> Lacy CF, Armstrong LL, Goldman MP, Lance LL. Lexi-Comp's Drug Information Handbook International 13<sup>th</sup> edition.

<sup>14</sup> Medsafe Datasheet, Dimetapp DM Drops Cough and Cold. Prepared 8 December 2008 <accessed 17 December 2009>

<sup>15</sup> BMJ Group and RPS Publishing. British National Formulary 57, London, United Kingdom. March 2009

Adverse effects with cough and cold medicines can occur as a result of adverse reactions and interactions at therapeutic doses, accidental ingestion by a child resulting in overdose, medication/dosing errors by parents and prescribers resulting in unintentional overdose or deliberate overdose.

Information sources used in the review of safety data included non-randomised trials, observational studies, meta-analyses and major reviews, published case series, data from national and international spontaneous adverse reactions centres, data from national and international poisons centres and individual case safety reports from pharmaceutical companies. Placebo-controlled randomised trials were obtained for this review. However none of the studies retrieved had safety end points.

Expectorants/mucolytics: the known adverse effects to guaifenesin include gastrointestinal discomfort, nausea, vomiting and urolithiasis (with abuse), haemorrhagic erosions, cardiotoxicity and abuse.

Antitussives: the known adverse effects to dextromethorphan and pholcodine include anaphylaxis, rash, constipation and central nervous system (CNS) effects such as drowsiness, fatigue, dizziness, dystonia, psychosis, hallucinations, serotonin syndrome, drug abuse and respiratory depression. The known effects of antitussive overdose in children include excitation, confusion, extrapyramidal effects and respiratory depression.

Non-substance-specific safety data: There is no reliable denominator data for poisons centre data and individual case safety reports (ICSRs - adverse reaction reports). In addition, data obtained from poisons centres and ICSRs are limited by incomplete reporting.

#### Poisons data:

United States: Data from the American Association of Poisons Control Centres showed that over a seven and a half year period, the number of contacts, exposures or cases for OTC cough and cold medicines in children under twelve years of age was 774,960. The reports included decongestants (48%), antihistamines (42%), antitussives (32%) and expectorants (9%). Only a small proportion of subjects experienced serious reactions.

Reasons for exposure to cough and cold medicines in children less than twelve years of age included inadequate measures to keep medicines out of the reach of children (including inappropriate storage and temporary opening) and therapeutic/medication errors (including incorrect dose, confused units of measure, more than one medicine containing the same ingredient, healthcare professional iatrogenic, ten-fold dosing error and incorrect form or concentration given and dispensed).

Reasons for fatal exposure to cough and cold medicines in children less than twelve years of age included adverse reactions, intentional misuse, malicious intent, therapeutic error, unintentional general and unknown reason.



United Kingdom: There were 100,000 calls received for OTC cough and cold medicines by the UK National Poisons Information Centre over a four year period. Two hundred and thirty children were admitted to hospital in the UK over a one year period, following consumption of cough and cold medicines.

New Zealand: From the data provided by the New Zealand National Poisons Centre of cases requiring medical referral, the greatest proportion of childhood reports (0-16 years of age) was in the two to six year age group. The medicines implicated were mostly single ingredient antihistamine preparations primarily indicated for allergy, including Phenergan<sup>®</sup> (81), Histafen<sup>®</sup> (50), Polaramine<sup>®</sup> and Polaramine Reptabs<sup>®</sup> (37), Sudomyl<sup>®</sup> (15) and isolated cases of exposure to other medicines.

### **Reports to regulatory authorities / pharmacovigilance centres:**

It was noted that most of the fatalities with cough and cold medicines in the US, Canada and Australia involved children under two years of age, with serious reactions at therapeutic doses occurring in children over the age of two years.

United Kingdom: Serious reports involving cough and cold medicines in children less than twelve years of age included a total of 397 reports for nasal decongestants, antihistamines, expectorants and antitussives. The main suspected adverse reactions were CNS related, with the exception of reports involving expectorants, where hypersensitivity was the main suspected adverse reaction.

Canada: Seventy six percent of Canadian reports of OTC cough and cold medicines involved children less than six years of age (111 out of 145), with fatalities reported only in children under two years of age.

United States: The US AERS database at the time of this presentation contained nine fatal reports with decongestants in children between two and six years of age and twenty eight fatal reports with antihistamines in children between two and six years of age. Deaths and serious CNS, cardiac and respiratory events have occurred with therapeutic doses and overdose. Convulsions were more common in children over the age of two years and more common after therapeutic doses than overdose, while serious cardiac and respiratory events occurred more often after overdose.

New Zealand: There are forty four reports in the Centre for Adverse Reactions Monitoring database associated with cough and cold medicines in children aged eighteen years and below. The majority of the reports were allergic or CNS adverse effects. Eight of the forty four reports involved serious reactions (two reports involved children two years of age and older). Less than twenty five percent of the reports in children involved overdose, however this may be underestimated as CARM does not usually receive data regarding overdose in ADR reports. Seven cases in children involved hospitalisation, including one life-threatening reaction (pulmonary oedema in a six year old male who overdosed with phenylephrine). No childhood deaths involving cough and cold medicines have been reported in New Zealand.

## Cough Cold Working Party conclusions on safety

The group noted that:

- Fatal reports of adverse drug reactions (ADRs) or overdose involving cough and cold medicines are very rare in children over two years of age.
- Serious ADR reports involving cough and cold medicines are rare in children over two years of age and there is widespread use of these medicines.
- Anaphylaxis is common to all the substances, while cardiovascular and CNS reactions are less likely with bromhexine and possibly guaifenesin. The inclusion of several substances with similar potential adverse effects in one medicine may increase the risk of these side effects in some children.
- Causes of overdose are of concern, but accidental childhood ingestion may often involve preparations purchased for adults, especially in New Zealand.

### 9 Potential for abuse or misuse

- Potential for misdiagnosis. The presentation and duration of the common cold in children is different from that exhibited by adults. Differential diagnoses for the common cold include the following: hay fever (allergic rhinitis), sinusitis (chronic), Streptococcal tonsillitis, sinusitis (acute), infectious mononucleosis, influenza, meningococcal disease, HIV seroconversion illness.<sup>16</sup>
- Pregnancy & lactation:<sup>17,18,19</sup>
  - Phenylephrine has been associated with haemorrhages and cardiovascular and limb malformations in animal models. Risk of ventricular septal defects was associated with decongestant use in pregnant women in one study. The vasoconstrictive effects of these drugs raise the hypothesis that their use in early pregnancy might increase the risk of vascular disruption defects. Decongestant use in the first trimester has been discussed in association with small increases in risks of gastroschisis, small intestinal atresia, and hemi-facial microsomia. The majority of decongestant use is in oral form, and the question of whether intranasal formulations carry risk has not been adequately addressed. Recommendation: systemic use of sympathomimetics should be avoided during pregnancy, inadvertent use is not an indication for the termination of pregnancy. Phenylephrine is classed as a B2 drug in the Australian categorization of prescribing medicines in pregnancy.
  - There is no evidence of an increased risk of congenital malformations or other adverse effects on pregnancy outcome from the use of guaifenesin.

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<sup>16</sup> <http://bestpractice.bmj.com/best-practice/monograph/252/diagnosis/differential.html> <accessed 21 December 2009>

<sup>17</sup> <http://www.tga.gov.au> <accessed 21 December 2009>

<sup>18</sup> <http://www.ukmicentral.nhs.uk> <accessed 21 December 2009>

<sup>19</sup> Schaefer C, Peters P.W.J., Miller R.K. Drugs, during pregnancy and lactation {electronic resource} 2<sup>nd</sup> ed. ISBN: 9780444520722

Guaifenesin is classed as a category A drug in the Australian categorization of prescribing medicines in pregnancy. Guaifenesin is probably also well-tolerated during breastfeeding but there are no systematic studies to date.

- There are no case reports on the use of dextromethorphan during breastfeeding. Dextromethorphan is classed as a category A drug in the Australian categorization of prescribing medicines in pregnancy.
- Ipecacuanha is classed as a category A drug in the Australian categorization of prescribing medicines in pregnancy.

[Category A = Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Category B2 = Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.]

- Potential for adult products to be used inappropriately in paediatric populations. This would be mitigated to some extent by restricting sale and supply of these products to a pharmacy where access to appropriate healthcare advice is enhanced. Some of this risk would also be mitigated by the packaging and labelling recommendations made in this submission.
- Dextromethorphan abuse: Prescription and over the counter cough and cold medication abuse is rapidly becoming a health concern. Dextromethorphan is a synthetic analogue of codeine and can produce psychoactive effects similar to that of marijuana (contributing to judgment impairment, injury or fatality). Higher doses will produce dissociative effects, including sensory enhancement and hallucinations. Data from surveys and poison control centre records demonstrate an increased nonmedical use of prescription and over-the counter cough and cold preparations, particularly those containing dextromethorphan. Abusers of dextromethorphan have developed a simple acid-base extraction technique to “free-base”, or extract the dextromethorphan from the unwanted guaifenesin, colouring agents, sweeteners, and alcohol that are typically included in combination cold preparations. Co-ingestion of other substances found in over-the-counter medications may also cause significant morbidity.<sup>20,21,22, 23</sup>

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<sup>20</sup> Cochems A, Harding P, Liddicoat L. Dextromethorphan in Wisconsin drivers. *J Anal Toxicol.* 2007 May; 31(4): 227-32 (abstract)

<sup>21</sup> Miller SC. Dextromethorphan psychosis, dependence and physical withdrawal. *Addict Biol.* 2004 Dec; 10(4): 327-7

<sup>22</sup> Hendrickson RG, Cloutier RL. “Crystal dex:” free-base dextromethorphan. *J Emerg Med.* 2007 May; 32(4): 393-6 Epub 2007 Apr 16

APPENDIX I:

**Excerpt from Medicines Classification Committee minutes – 14 May 2009, for the committee's reference.**

***Guaiphenesin (Mucinex, Reckitt Benckiser)***

*This is a company submission for the reclassification from prescription medicine to general sales medicine of 600 mg and 1200 mg modified release guaiphenesin tablets for use as an expectorant to help relieve chest congestion. Guaiphenesin is currently a general sale medicine when for oral use in medicines containing 2% or less or 200 mg or less per dose form.*

*There appeared to be few safety issues associated with the use of guaiphenesin and the modified release dose form had been available OTC in the United States for 6-7 years. Nevertheless, the Committee was aware of a potential clinical risk of developing kidney stones at higher doses and considered that a warning about this should be included. It was also noted that guaiphenesin was not appropriate for patients with porphyria, though the incidence of this is low in New Zealand and a warning on the label was not essential.*

*The Committee discussed other warning statements and agreed that the sponsor's statement of "seek medical advice if your cough worsens or does not go away after a few days" was too vague. They recommended seeking medical advice if symptoms persist "after three days".*

*Additional label warning statements proposed by the sponsor, and supported by the Committee, included "Do not give to children under 12 years of age" and "Do not exceed the stated dose".*

*The submission had proposed pack sizes of up to 100 tablets. This quantity was deemed excessive for distribution as a general sale medicine. Anyone requiring that much medication to treat a cough should consult a doctor. Limiting the pack size to a 5 day supply was thought to be more appropriate. This would be in line with the pack sizes of immediate release medicines containing guaiphenesin that were already available for general sale. A limited pack size could also reduce the risk of self-medicating for off-label use, such as in those suffering from fibromyalgia.*

*The issue of a modified release dose form being available as a general sale medicine for treating coughs and colds was discussed but, ultimately, was not deemed to pose an obstacle to the medication being classified at this level.*

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<sup>23</sup> Levine DA. "Pharming": the abuse of prescription and over-the-counter drugs in teens. *Curr Opin Pediatr.* 2007 Jun; 19(3): 270-4  
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*Guaiifenesin's efficacy in a modified release dose form was also discussed. The Committee was assured by the Chairman that the sponsor would need to provide Medsafe with satisfactory efficacy data as part of the process of applying for consent to distribute the medicine in New Zealand.*

*In conclusion, the Committee felt that the submission was largely satisfactory. The Committee recommended reclassifying guaiphenesin in modified release dose form to general sale, with limits on pack size and daily intakes. Relevant warning statements, including those discussed above, should also be included on the packaging.*

### ***Recommendation***

*That guaiphenesin should be reclassified from prescription medicine to general sale medicine when:*

- pack size is limited to not more than 5 days' supply*
- in a modified release dosage form*
- a maximum daily dose of not more than 2400 mg is recommended*
- sold in packs approved by the Minister or the Director-General for distribution as general sale medicines.*

*That guaiphenesin should be reclassified from prescription medicine to restricted medicine when:*

- pack size is more than 5 days' but not more than 30 days' supply*
- in a modified release dosage form*
- a maximum daily dose of not more than 2400 mg is recommended*
- sold in packs approved by the Minister or the Director-General for distribution as restricted medicines.*

*That Medsafe should be satisfied with data supporting efficacy, and with the proposed label warnings, of any modified release guaiphenesin product seeking consent to be sold as an OTC medicine.*

## APPENDIX II:

### **Micromedix summary of adverse reaction information in the population in general i.e. not specifically paediatric populations:**

#### Dextromethorphan:

Adverse effects with dextromethorphan appear to be rare and may include dizziness and gastrointestinal disturbances. Excitation, confusion, and respiratory depression may occur after overdosage. Dextromethorphan has been subject to abuse, but there is little evidence of dependence of the morphine type.<sup>24</sup>

Hypersensitivity: A fixed-drug reaction developed in a patient after ingestion of dextromethorphan 30 mg. Oral provocation with dextromethorphan produced a positive reaction but the results of topical application tests were negative. Urticaria, angioedema, and shortness of breath were reported in another patient;<sup>2</sup> symptoms recurred on oral challenge, but no skin test was performed. Similar symptoms were reported in a third patient;<sup>3</sup> skin testing provoked a positive reaction. On oral rechallenge, the patient developed urticaria initially, followed by generalised erythema and pruritus and decreased blood pressure after a second dose.<sup>25,26,27</sup>

Overdose: There have been reports of overdosage or accidental poisoning (usually in children) due to dextromethorphan, including rare fatalities. Naloxone may be effective in reversing toxicity. Extrapyramidal reactions were seen in a child who ingested dextromethorphan. Overdosage has also been associated with abuse.<sup>28,29,30,31,32,33,34</sup>

#### Guaifenesin

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<sup>24</sup> Bem JL, Peck R. Dextromethorphan: an overview of safety issues. *Drug Safety* 1992; 7: 190-9. (PubMed id:1503667)

<sup>25</sup> Stubb S, Reitamo S. Fixed-drug eruption due to dextromethorphan. *Arch Dermatol* 1990; 126: 970-1. (PubMed id:2141783)

<sup>26</sup> Knowles SR, Weber E. Dextromethorphan anaphylaxis. *J Allergy Clin Immunol* 1998; 102: 316-17. (PubMed id:9723677)

<sup>27</sup> Robledo T, et al. Adverse reaction to dextromethorphan. *Allergy* 2004; 59: 890. (PubMed id:15230826)

<sup>28</sup> Shaul WL, et al. Dextromethorphan toxicity: reversal by naloxone. *Pediatrics* 1977; 59: 117-19. (PubMed id:840529)

<sup>29</sup> Katona B, Wason S. Dextromethorphan danger. *N Engl J Med* 1986; 314: 993. (PubMed id:3960067)

<sup>30</sup> Rammer L, et al. Fatal intoxication by dextromethorphan: a report on two cases. *Forensic Sci Int* 1988; 37: 233-6. (PubMed id:3410392)

<sup>31</sup> Schneider SM, et al. Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; 9: 237-8. (PubMed id:2018593)

<sup>32</sup> Pender ES, Parks BR. Toxicity with dextromethorphan-containing preparations: a literature review and report of two additional cases. *Pediatr Emerg Care* 1991; 7: 163-5. (PubMed id:1876508)

<sup>33</sup> Warden CR, et al. Dystonic reaction associated with dextromethorphan ingestion in a toddler. *Pediatr Emerg Care* 1997; 13: 214-15. (PubMed id:9220509)

<sup>34</sup> Roberge RJ, et al. Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; 17: 285-8. (PubMed id:10195488)

Gastrointestinal discomfort, nausea, and vomiting have occasionally been reported with guaifenesin, particularly in very large doses.

Abuse: Urinary calculi have been reported in patients consuming large quantities of over-the-counter preparations containing guaifenesin.<sup>35,36</sup> Spectroscopic analysis revealed that the stones were composed of a calcium salt of beta-(2-methoxyphenoxy)-lactic acid, which is a metabolite of guaifenesin. Small quantities of ephedrine were also present in the stones of one of several patients who had ingested preparations containing a combination of guaifenesin and ephedrine.

Porphyria: Guaifenesin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals.

### Ipecacuanha

Large doses of ipecacuanha have an irritant effect on the gastrointestinal tract, and persistent bloody vomiting or bloody diarrhoea may occur. Mucosal erosions of the entire gastrointestinal tract have been reported. The absorption of emetine, which is most likely if vomiting does not occur after emetic doses of ipecacuanha may give rise to adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These, combined with dehydration due to vomiting may cause vasomotor collapse followed by death. There have been several reports of chronic abuse of ipecacuanha to induce vomiting in eating disorders; cardiotoxicity and myopathy have occurred and may be a result of accumulation of emetine.

There have also been several reports of ipecacuanha poisoning due to the unwitting substitution of Ipecac Fluidextract (a former USP preparation) for Ipecac Syrup (USP); the fluidextract was about 14 times the strength of the syrup.<sup>37</sup>

Hypersensitivity: Allergy, characterized by rhinitis, conjunctivitis, and chest tightness, has occurred due to inhalation of ipecacuanha dust in packers of ipecacuanha tablets.<sup>38</sup>

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<sup>35</sup> Pickens CL, et al. Abuse of guaifenesin-containing medications generates an excess of a carboxylate salt of beta-(2-methoxyphenoxy)-lactic acid, a guaifenesin metabolite, and results in urolithiasis. *Urology* 1999; 54: 23-7. (PubMed id:10414721)

<sup>36</sup> Assimos DG, et al. Guaifenesin- and ephedrine-induced stones. *J Endourol* 1999; 13: 665-7. (PubMed id:10608519)

<sup>37</sup> Manno BR, Manno JE. Toxicology of ipecac: a review. *Clin Toxicol* 1977; 10: 221-42. (PubMed id:15766)

<sup>38</sup> Luczynska CM, et al. Occupational allergy due to inhalation of ipecacuanha dust. *Clin Allergy* 1984; 14: 169-75. (PubMed id:6142776)

Vomiting: Prolonged vomiting has been reported in seventeen percent of patients given ipecacuanha in the treatment of poisoning and may lead to gastric rupture, Mallory-Weiss tears of the oesophagogastric junction, cerebrovascular events, and pneumomediastinum and pneumoperitoneum.<sup>39</sup>

### Phenylephrine:

Phenylephrine has mainly alpha-agonist effects. It has a longer duration of action than noradrenaline and an excessive vasopressor response may cause a prolonged rise in blood pressure. It induces tachycardia or reflex bradycardia and should therefore be avoided in severe hyperthyroidism and used with caution in severe ischemic heart disease. Patients with diabetes mellitus or prostatic hyperplasia should also avoid phenylephrine.

Since phenylephrine is absorbed through the mucosa systemic effects may follow application to the eyes or the nasal mucosa. In particular, phenylephrine ten percent eye drops can have powerful systemic effects. They should be avoided or only used with extreme caution in infants, the elderly, and in patients with cardiac disease, significant hypertension, or advanced arteriosclerosis. Fatalities have been reported in patients with pre-existing cardiovascular disease.

Use of phenylephrine in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients. Ophthalmic solutions of phenylephrine are contra-indicated in patients with angle-closure glaucoma. Corneal clouding may occur if corneal epithelium has been denuded or damaged.

Excessive or prolonged use of phenylephrine nasal drops can lead to rebound congestion. Phenylephrine hydrochloride is irritant and may cause local discomfort at the site of application; extravasation of the injection may even cause local tissue necrosis.

Effects on the cardiovascular system: Systemic adverse effects have occurred after the use of phenylephrine as eye drops (particularly at a strength of ten percent), or nasal drops.

Hypertension<sup>40</sup> and hypertension with pulmonary oedema<sup>41</sup> have been described in infants and children after the use of phenylephrine ten percent eye drops. Hypertension with arrhythmias has also been reported in an eight year-old child<sup>42</sup> and in an adult<sup>43</sup> after phenylephrine ten percent eye drops had been used. Details have also been published on a

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<sup>39</sup> . Bateman DN. Adverse reactions to antidotes. Adverse Drug React Bull 1988; 133: (Dec.): 496-9.

<sup>40</sup> Borromeo-McGrail V, et al. Systemic hypertension following ocular administration of 10% phenylephrine in the neonate. Pediatrics 1973; 51: 1032-6. (PubMed id:4575724)

<sup>41</sup> Baldwin FJ, Morley AP. Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops. Br J Anaesth 2002; 88: 440-2. (PubMed id:11990281)

<sup>42</sup> Vaughan RW. Ventricular arrhythmias after topical vasoconstrictors. Anesth Analg 1973; 52: 161-5. (PubMed id:4735272)

<sup>43</sup> Lai Y-K. Adverse effect of intraoperative phenylephrine 10%: case report. Br J Ophthalmol 1989; 73: 468-9. (PubMed id:2751981)



series of thirty two patients who had systemic cardiovascular reactions, including fatal myocardial infarctions, after the use of phenylephrine 10% solutions in the eye.<sup>44</sup> Severe cardiovascular adverse reactions have also been reported to the use of phenylephrine as topical 10% ocular<sup>45</sup> or 0.25% nasal<sup>46</sup> pledgets. Although the incidence of such reactions seems low,<sup>47</sup> the use of lower concentrations<sup>1,5</sup> and caution in susceptible patients such as those with cardiovascular disorders or the elderly,<sup>5</sup> have been advocated. A reduction in the eye-drop volume has been found to produce adequate mydriasis and may reduce systemic absorption and the risk of adverse cardiovascular effects.<sup>48,49</sup>

Effects on the eyes: Acute and chronic conjunctivitis has been reported<sup>50</sup> after use of over-the-counter ophthalmic decongestant preparations of phenylephrine, naphazoline, or tetrahydrozoline. The conjunctival inflammation took several weeks to resolve in some cases. Dermatoconjunctivitis<sup>51</sup> has also been reported after use of phenylephrine eye drops.

Effects on mental function: Hallucinations and paranoid delusions have been reported<sup>52</sup> in a patient after excessive use of a nasal spray containing phenylephrine 0.5%. Mania has also followed the use of large oral doses.<sup>53</sup>

Hypersensitivity: Cross-sensitivity to phenylephrine has been reported in a patient hypersensitive to pseudoephedrine.<sup>54</sup>

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<sup>44</sup> . Fraunfelder FT, Scafidi AF. Possible adverse effects from topical ocular 10% phenylephrine. *Am J Ophthalmol* 1978; 85: 447-53. (PubMed id:655224)

<sup>45</sup> Fraunfelder FW, et al. Adverse systemic effects from pledgets of topical ocular phenylephrine 10%. *Am J Ophthalmol* 2002; 134: 624-5. (PubMed id:12383833)

<sup>46</sup> . Hecker RB, et al. Myocardial ischemia and stunning induced by topical intranasal phenylephrine pledgets. *Mil Med* 1997; 162: 832-5. (PubMed id:9433094)

<sup>47</sup> Brown MM, et al. Lack of side effects from topically administered 10% phenylephrine eyedrops: a controlled study. *Arch Ophthalmol* 1980; 98: 487-9. (PubMed id:7362505)

<sup>48</sup> Craig EW, Griffiths PG. Effect on mydriasis of modifying the volume of phenylephrine drops. *Br J Ophthalmol* 1991; 75: 222-3. (PubMed id:2021589)

<sup>49</sup> Wheatcroft S, et al. Reduction in mydriatic drop size in premature infants. *Br J Ophthalmol* 1993; 77: 364-5. (PubMed id:8318484)

<sup>50</sup> . Soparkar CN, et al. Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. *Arch Ophthalmol* 1997; 115: 34-8. (PubMed id:9006422)

<sup>51</sup> . Moreno-Ancillo A, et al. Allergic contact reactions due to phenylephrine hydrochloride in eyedrops. *Ann Allergy Asthma Immunol* 1997; 78: 569-72. (PubMed id:9207720)

<sup>52</sup> Snow SS, et al. Nasal spray 'addiction' and psychosis: a case report. *Br J Psychiatry* 1980; 136: 297-9. (PubMed id:6155964)

<sup>53</sup> . Waters BGH, Lapierre YD. Secondary mania associated with sympathomimetic drug use. *Am J Psychiatry* 1981; 138: 837-40. (PubMed id:6166211)

<sup>54</sup> Buzo-Sanchez G, et al. Stereoisomeric cutaneous hypersensitivity. *Ann Pharmacother* 1997; 31: 1091. (PubMed id:9296255)