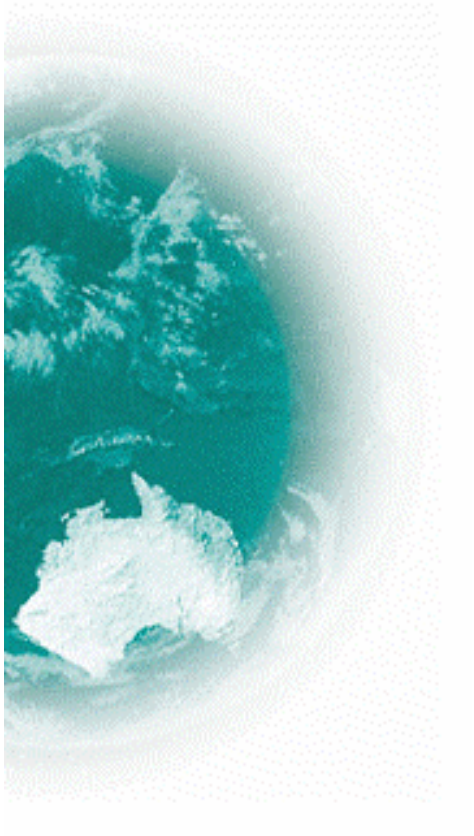
Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

TGA internal panel report on the safety, efficacy and use of cough and cold medicines in the treatment of children aged 2-12 years



May 2009

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1. Introduction

Since late 2007 the drug regulatory authorities in Canada, the USA, the United Kingdom, New Zealand and Australia have taken regulatory action to restrict the availability and use of cough and cold medicines for the treatment of young children. These actions have been taken in stages and after careful consideration of the available data and each country's own circumstances and experience. In some cases reviews are currently ongoing and further action is being considered.

There have been numerous releases of information and advisories through regulatory authority websites and other media outlets, and the TGA has monitored these developments carefully.

At first, the regulators' attention was focused on the safety of cough and cold medicines containing sedating antihistamines when used in children aged under 2 years. By early 2008 all five agencies had taken regulatory action to stop or strongly discourage the use of these medicines in children aged under 2 years.

Attention was then extended to the use in children aged under 2 years of other over-the-counter (OTC) cough and cold medicines containing non-sedating antihistamines, antitussives, expectorants or decongestants. The outcome was that all five agencies determined that none of these medicines should be used in children aged under 2 years.

Reviews were then widened to consider the safety and efficacy of cough and cold medicines in children aged 2-12. All five regulatory agencies have come to the conclusion that there is a clear lack of robust evidence for the efficacy of any of these medicines for the treatment of young children and that their use can cause significant risks of serious side effects. However, the different regulators have followed slightly different approaches to managing the risk-benefit profiles of these medicines.

The current situation (May 2009) is as follows:

- **Canada:** Health Canada's Therapeutic Products Directorate (TPD) has concluded that cough and cold medicines should not be used in children under 6 years of age and that these products should be labelled accordingly.
- **The UK:** The MHRA has concluded that cough and cold medicines should not be used in children under 6 years of age and that these products should be labelled accordingly, and as from March 2009 all cough and cold medicines (other than senega and ammonia) and intended for treatment of children aged 6-12 years will be classified as "pharmacy only medicines". In addition, the MHRA has concluded that these medicines should not be recommended for children aged 6-12 years. It has also determined that all liquid cough and cold medicines containing the ingredients it has reviewed must be in child resistant containers.
- **The USA:** The FDA has strongly endorsed voluntary moves by the US pharmaceutical industry to label cough and cold medicines with a warning that they should not be used in children under 4 years of age. It also advises parents and caregivers to choose OTC cough and cold medicines with child-proof safety caps, when available, and to store the medicines out of the reach of children.
- **New Zealand:** Medsafe has determined that cough and cold medicines should not be used in children under 2 years of age and has instructed sponsors to label (or over-label) these products accordingly. Medsafe is still considering what, if any, additional action it needs to take concerning children aged 2 years and above. It intends to review additional information from the MHRA and the TPD to determine if it should follow their decisions to advise against use of these medicines in children under 6 years. In the meantime Medsafe is advising parents and caregivers to exercise extra care when using these medicines to treat children in that age group.

- **Australia:** The TGA has determined that cough and cold medicines should not be used in children under 2 years of age and has instructed sponsors to label these products accordingly. It will take a year or two for current stock to be used up and for all stock on pharmacy shelves to carry the required warnings.

  The TGA has obtained relevant detailed information "in confidence" from the MHRA and the TPD on their reviews of safety and efficacy data but has also received the findings of its own independent external review of the information available in the open literature along with other information provided by sponsors. It has also analysed the adverse drug reaction reports in its data base relating to cough and cold medicines used for the treatment of children.

  The TGA is now in a position to consider the results of its own external review and its analysis of its own adverse drug reaction data together with the results of similar reviews, analyses and regulatory actions by its overseas counterparts and to determine what, if any, action it needs to take to modify the availability and usage of cough and cold medicines for children aged 2 years and over.

  In the meantime the TGA has issued warnings and advice about the use of cough and cold medicines for treating children in a way that minimises the risk of adverse effects.

  All of the cough and cold medicines included in this review (apart from senega and ammonia mixture) and currently available for children aged 2 years and older are scheduled as S2 (pharmacy only) medicines and, thus, professional advice on their appropriate usage is at least available to consumers.

2. The drugs reviewed

The ranges of drugs used in cough and cold medicines differ from country to country. Consequently, each of the four regulatory agencies who have reviewed their usage in children has needed to consider the drugs used in its own particular country. The TGA review has considered the available data for each of the 21 drug substances used in oral and topical nasal cough and cold medicines registered in Australia and used in products available in the marketplace to be used for the treatment of children in this country.

There are differences in the drugs available and also the ways OTC medicines are regulated and distributed via pharmacies or general retail outlets in the different countries. Therefore, it was important that the TGA carry out its own review rather than simply adopt the findings and conclusions of its overseas counterparts. However, there is sufficient overlap between the list of drugs reviewed in Australia and those reviewed in Canada, the UK and the USA for the overseas assessments to be of significant relevance to the TGA's review.

The drugs available and reviewed in Australia and other countries are listed in the table below. Note that in some cases the drugs exist in different salt forms but the pharmacological activity is due to the drug moiety and, hence, the neutral forms and salts have been grouped together. The drugs available in OTC cough and cold medicines in Australia are shown in bold type.

Oxymetazoline is available in Australia only as nasal drops and nasal spray. Xylometazoline is available only as eye drops, nasal drops and nasal spray. The other drugs reviewed are available as oral liquids and/or tablets and/or capsules.

DRUG	Australia (TGA)	Canada (TPD)	UK (MHRA)	USA (FDA)
ANTIHISTAMINES:				
Brompheniramine	✓	✓	✓	✓
Chlorpheniramine	✓	✓	✓	✓
Dexchlorpheniramine	✓			✓
Diphenhydramine	✓	✓	✓	✓
Doxylamine	✓	✓		✓
Pheniramine	✓	✓		✓
Promethazine	✓	✓		
Triprolidine	✓	✓		✓
Chlorcyclizine				✓
Clemastine		✓		
Dexbrompheniramine		✓		✓
Diphenylpyraline		✓		
Phenindamine				✓
Phenyltoloxamine		✓		
Pyrilamine maleate		✓		✓
Thonzylamine hydrochloride				✓
ANTITUSSIVES:				
Codeine	✓	✓		✓
Dextromethorphan	✓	✓	✓	✓
Dihydrocodeine	✓			
Pentoxyverine	✓			
Pholcodine	✓		✓	
Clophendianol		✓		✓
Diphenhydramine		✓		✓
MUCOLYTICS/EXPECTORANTS:				
Ammonium chloride	✓			
Bromhexine	✓			
Guaifenesin	✓	✓	✓	✓
Ipecacuanha	✓		✓	
Senega and ammonia	✓			
DECONGESTANTS:				
Oxymetazoline	✓		✓	✓
Phenylephrine	✓	✓	✓	✓
Pseudoephedrine	✓	✓	✓	✓
Xylometazoline	✓		✓	✓
Epinephrine				✓
Levmatamfetamine				✓
Naphazoline				✓
Propylhexedrine				✓
Racephedrine				✓
Racepinephrine				✓

3. Summary of the TGA External Review

The TGA's independent review by external experts was conducted to assess the efficacy and safety of cough and cold medications in common use in Australia. The key findings of this review are as follows:

(i) There is currently a strong demand for OTC cough and cold medicines for the treatment of children and that demand has been regarded as evidence of their effectiveness.

(ii) The available clinical data does not support the efficacy of these medicines in children.

(iii) The use of these medicines in children has been the cause of significant adverse reactions, including death.

The reviewers suggest that the following three options be considered for addressing the implications of these findings:

(i) Take no action and maintain the 'status quo'.

(ii) Take rigid action based strictly on evidence and exclude the use of these drugs for children in age groups (e.g., under 6 years) where there is a lack of evidence of efficacy but there is a safety hazard and the risks outweigh the benefits.

(iii) Take what actions that may be needed to reduce or eliminate hazards, but await the availability of further clinical data generated to current standards about efficacy of these medicines in children before determining if the presence or absence of efficacy can be established.

4. Adverse drug reactions reported to the TGA

Since 1981 there have been 99 ADRs reported in children under the age of 12 (promethazine and codeine were excluded when clearly not used for the symptomatic relief of coughs and colds).

Of these 99 ADRs:

- 86 (87%) occurred in children under the age of 9
- 71 (72%) occurred in children under the age of 6
- The mean number of ADRs was 12 per year for children under 6, and 4 per year for children between 6 and 12 years of age

14 (14%) of ADRs were classified as "serious". Of these:

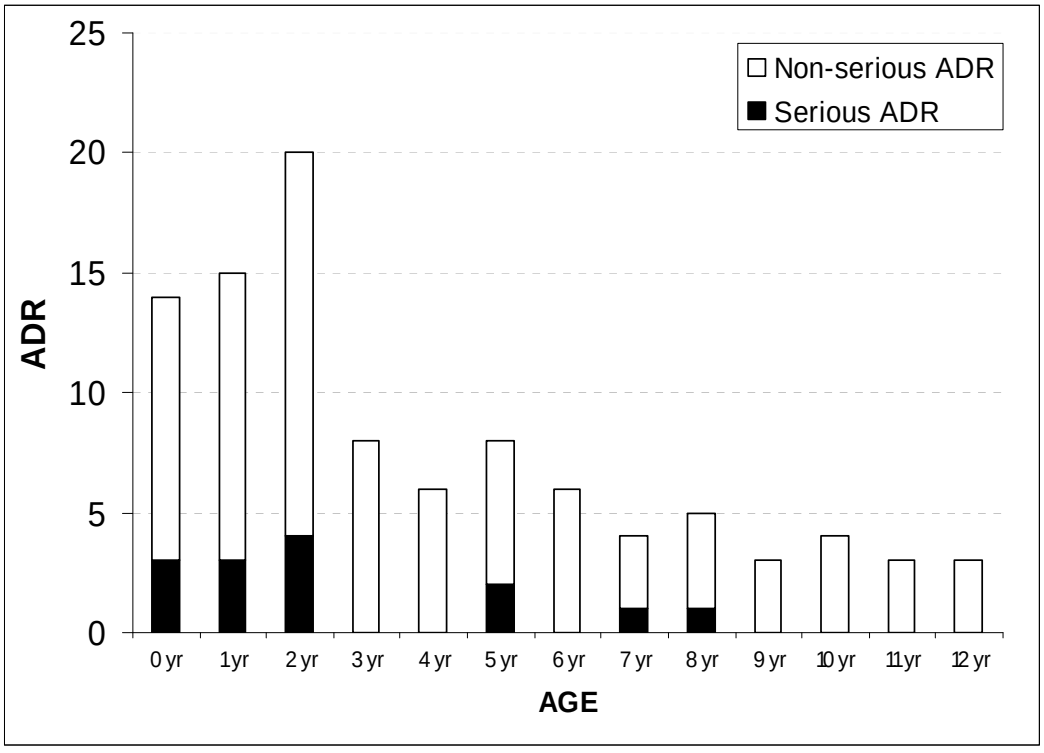
- 12 (86%) of serious ADRs occurred in under 6 yrs
- 1 (7%) was assigned probable causality, 10 (71%) were assigned possible causality and in 3 cases (22%) causality was "unclear".

2 deaths were included in the 14 serious ADRs, as follows:

- The first occurred in a 1 year old infant administered oxymetazoline and morphine
- The second death occurred in a 2 year old child administered ipecacuanha (unclear whether ipecacuanha used for its expectorant or emetic properties) in combination with other medications

In addition to the ADRs, 2 intentional and 2 accidental overdoses were reported.

The following graph shows the number of serious (black), non-serious (white), and total number of ADRs reported for children aged 12 and under between 1981 and 2009.



The following table shows the number of serious, non-serious, and total number of ADR for children aged 12 and under between 1981 and 2009 for each therapeutic agent. Serious and non-serious ADRs were reported for all classes of cough and cold medications. Numbers in brackets refer to ADR when used in combination with another cough and cold medication.

Drug available in Australia	No ADR (Total)	No ADR (Serious)
ANTIHISTAMINES:		
Brompheniramine maleate	0	0
Chlorpheniramine maleate	1	1 (1)
Dexchlorpheniramine maleate	13	3
Diphenhydramine hydrochloride	(1)	0
Doxylamine succinate	0	0
Pheniramine maleate	0	1
Promethazine hydrochloride	3 (5)	0
Triprolidine hydrochloride	0	0
ANTITUSSIVES:		
Codeine phosphate	(1)	0
Dextromethorphan hydrobromide	10 (2)	2
Dihydrocodeine tartrate	0 (1)	0
Pentoxyverine citrate	0	0
Pholcodine	15	1
MUCOLYTICS/EXPECTORANTS:		
Ammonium chloride	0	0
Bromhexine hydrochloride	10 (2)	1
Guaifenesin (guaiphenesin)	3	0
Ipecacuanha	3	1
Senega & ammonia (as bicarbonate)	0	0
DECONGESTANTS:		
Oxymetazoline hydrochloride	9	2
Phenylephrine hydrochloride	(1)	(1)
Pseudoephedrine hydrochloride	18 (4)	2
Xylometazoline hydrochloride	1	0
TOTAL	**86 (17)**	**13 (2)**

5. Discussion

Safety and efficacy

The risk/benefit ratio of cough and cold preparations administered to children is difficult to ascertain. The TGA external review identified a lack of efficacy data and a potential for significant adverse reaction relating to the use of cough and cold preparations in children. The report highlighted the strong demand for OTC cough and cold products intended for use in children and proposed three options for regulators.

The first of these options involved maintaining the "status quo", the second involved a precautionary, evidence based approach whereby the use of medications would be available only to populations where the benefit outweighed potential risks, the third option proposed that essential steps could be taken to minimize potential hazards whilst more robust efficacy data become available.

Regulators in Canada, the UK, the USA and New Zealand have been faced with similar options. The approach in the UK and Canada has been to exclude cough and cold products for children under 6 years of age based upon an unfavourable risk/benefit ratio in that age group. The approach in the USA has been to exclude cough and cold products for children under 4 years of age whilst supporting the generation of robust efficacy data.

Cough and cold preparations have a relatively safe history of use in children exposed to cough and cold medicines Australia with only 99 ADRs reported since 1981 for children aged 12 years or under. However, 14 serious reactions (1 probable, 10 possible, 3 unclear) occurred during this period, and so the risks of cough and cold preparations administered to children cannot be considered negligible. Furthermore, the number of adverse reactions must be considered within a context that includes a population that is small relative to many other countries. For this reason we must take into account the experiences of larger countries with cultures and regulatory practices most similar to our own. The Australian regulatory environment for OTC cough and cold products in children is similar to that of Canada and the UK and somewhat more restrictive than that of the USA and it is of note that the pattern of reported ADRs for children exposed to cough and cold preparations closely resembles those observed in Canada and the UK.

Current warnings advise against the use of cough and cold preparations in children under the age of 2. However it is clear that a significant number of ADRs were reported for children above 2 years, in fact the highest number of ADRs occurred for children 2 years of age. A majority of ADRs reported to the TGA occurred in children under the age of 6. The explanation for this is likely to be multifactorial but may include the following:

- Inappropriate use: assessing symptoms in young children can be difficult. Young children are also limited in their ability to communicate their need for treatment and the effects of treatment.
- Inappropriate dosing: dosing requirements of younger children may be weight, rather than age, dependent. A large degree of overlap is seen for population-based weight charts of younger children. Doses based on age that reflect population averages may be inappropriate for some children.
- Uncertainty regarding compliance may exist depending on the degree of parental supervision. Lack of efficacy may be assumed to be due to lack of compliance, leading to further dosing.
- An increased number of coughs and colds in this age group.

Packaging

Therapeutic Goods Order No. 80 "*Child-Resistant Packaging Requirements for Medicines*" (1980) requires that the containers for all oral liquid medicines containing any of the antihistamines, the antitussives codeine or dihydrocodeine, or the decongestants phenylephrine or pseudoephedrine must have child-resistant closures. TGO 80 does not require child-resistant closures for the antitussives dextromethorphan or pholcodine, or the expectorants guaifenesin or ipecacuanha. However, these four drugs have caused significant numbers of ADRs in children in Australia and/or overseas and there appears to be no good reason why they should not also be in child-resistant packaging.

Topical nasal decongestants

Oxymetazoline and Xylometazoline are available in Australia as nasal drops and nasal sprays and eye drops. They are not available as oral medicines.

The Medicines Evaluation Committee should specifically consider whether the recommendations should apply to topical nasal decongestants for relief of symptoms of colds.

6. Recommendations

Safety, efficacy and availability

In light of the current lack of evidence of efficacy and the historical profile of ADRs in Australia and overseas, it is likely that the risks associated with the use of cough and cold preparations in children outweigh the likely benefits for children below the age of 6 years. There is currently a lack of evidence of efficacy for cough and cold medicines in children aged 6 to 12 years of age and the historical profile of ADRs indicates that there are potential risks involved in use of these medicines in that age group also. For this reason,

> **it is recommended that over-the-counter cough and cold medicines should not be used for the treatment of children under 6 years of age, and they should only be administered to children aged 6-12 years on the advice of a doctor or pharmacist.**

To this end, it is recommended that:

> **the labelling of over-the-counter cough and cold medicines should not include dosage instructions for children under 6 years of age;**
>
> **if doses are included for children aged 6-11 years, the labelling must include:**
>
> **(a) a warning statement advising against use in children under the lowest specified age, AND**
>
> **(b) a statement advising that the product should only be administered to children between the lowest specified age and 12 years on the advice of a doctor or pharmacist; and**
>
> **the labelling of all over-the-counter cough and cold medicines with dosage specified only for adults and/or for those aged 12 and above should contain a warning statement specifically advising against their use in children under 12 years of age.**

This approach would bring the regulation of cough and cold preparations in Australia into line with measures in place in the UK and Canada. The need for such limitations on use in children should be reviewed if and when robust efficacy data becomes available.

Packaging

The current requirements under TGO 80 are for most, but not all, of the drugs in OTC liquid cough and cold medicines to be in child-resistant packaging. In the interests of consistency and improved safety,

> **it is recommended that over-the-counter cough and cold medicines should be marketed in containers with child-resistant closures.**

This requirement would bring the packaging of cough and cold preparations in Australia into line with measures in place in the UK and with recommendations made by the regulators in the USA.

Scheduling

The current scheduling of most cough and cold medicines as S2 (pharmacy only) medicines ensures that advice is available but does not ensure that such advice is given regarding use in children. Such advice is more likely to be given if these medicines were S3 (pharmacist only) medicines. For this reason,

> **it is recommended that the NDPSC be asked to consider including substances used in cough and cold medicines in Schedule 3 when intended for use in children aged 6-12 years, and in Schedule 4 for use in children under 6 years of age.**

Public awareness

The changes recommended above would need to be widely promoted and explained to medical practitioners, pharmacists, parents and caregivers. For this reason,

> **it is recommended that particular efforts be directed towards educating consumers, medical practitioners and pharmacists that OTC cough and cold medicines have not been shown to be effective, and are potentially harmful in children under 6 years of age. Education campaigns should be directed through the National Prescribing Service (NPS), professional colleges such as the Royal Australian College of General Practitioners, Australian College of Rural and Remote Medicine and the Royal Australian College of Physicians Paediatrics and Child Health Division, Pharmacy Guild, Consumers Health Forum and the pharmaceutical industry.**