



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Minutes

TGA Internal Panel to review cough and cold medicines for children aged 2-12 years

Executive Conference Room
25 June 2009

Present

Dr Ruth Lopert (Chair)
Dr Jane Cook
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Dr Gary Lacey
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Dr Peter Bird (Observer)
Ms Janet Ramsay (Minutes Secretary)

Background

The Panel was requested to consider a review on the safety, efficacy and availability of cough and cold medicines for the treatment of children. A TGA paper, prepared by the OTC Medicines Section and comprising the following information, was provided to the Panel:

- The TGA's *Draft report on a review of the safety, efficacy and use of cough and cold medicines in the treatment of children* ('TGA paper') included a brief summary of relevant regulatory actions and the current status in Australia, Canada, the UK, the USA and New Zealand, a summary of an External Review on cough and cold medicines, an analysis of adverse drug reactions reported in Australia, and tentative recommendations for regulatory action¹.
- Attachment 1: An external review prepared for the TGA by Dr XXXX and Professor XXXX, *Review of cough and cold medicines in Australia* (April 2009) [external Reviewers' Report], of the safety and efficacy of cough and cold medicines in children aged 2-12 years, using published papers and other data supplied by the TGA and sponsors. This review does not cover listed complementary medicines.
- Attachment 2: A more detailed chronological summary of reviews and regulatory actions undertaken to date in Australia, Canada, the UK, USA and New Zealand (additional information relating to this document was available at the meeting).

The sedating antihistamines are currently in Schedule 4 ('Prescription only medicine') when indicated for children under 2 years of age. While other active ingredients in cough and cold medicines are not currently scheduled on the basis of age of the user, the TGA has instructed

¹ Note: The TGA Draft Report has been revised to incorporate changes discussed at the Panel's meeting.

sponsors to label all cough and cold medicines to indicate that the products should not be used in children under 2 years of age, and is currently reviewing the use of cough and cold medicines in children aged 2 years and over. In the meantime, the TGA has issued advice on the use of all cough and cold medicines which aims to minimise the risk of adverse effects.

Health Canada and the MHRA (UK) have concluded that cough and cold medicines should not be used in children under 6 years of age and that products should be labelled accordingly. The MHRA has also concluded that these products should not be recommended for children aged 6-12 years, all cough and cold medicines (other than senega and ammonia) intended for treatment of children aged 6-12 years will be classified as 'pharmacy only medicines', and liquid cough and cold medicines must be packaged in child-resistant containers. The FDA (USA) has endorsed voluntary moves by the pharmaceutical industry to label cough and cold medicines with a warning that the products should not be used in children under 4 years of age. Medsafe (New Zealand) has determined that cough and cold medicines should not be used in children under 2 years of age, and intends to review information from the MHRA and Health Canada before making a decision in relation to use in children under 6 years.

The TGA paper noted the following substances that are included in cough and cold medicines in Australia:

- *Antihistamines*: brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine, triprolidine;
- *Antitussives*: codeine, dextromethorphan, dihydrocodeine, pentoxyverine, pholcodine;
- *Mucolytics/expectorants*: ammonium chloride, bromhexine, guaiphenesin, ipecacuanha, senega and ammonia;
- *Decongestants*: phenylephrine, pseudoephedrine, oxymetazoline, xylometazoline.

Some other substances are included in cough and cold medicines in Canada, the UK, USA and New Zealand.

A brief summary of adverse drug reaction (ADR) reports to the TGA indicated that 90 ADRs associated with the use of these substances for coughs and colds in children 12 years or under have been reported since 1981. Of these, 87% occurred in children under 9 years of age, and 70% in children under 6 years. Nine of the 11 ADRs classified as 'serious' were in children aged under 6 years. One death was reported in a 2 year old child administered ipecacuanha.

The [External Reviewers' Report] had identified a lack of efficacy data and the potential for significant adverse reactions associated with use of cough and cold medicines in children, and suggested three options for consideration by regulators – (i) take no action; (ii) take rigid action, based strictly on evidence, and exclude use in age groups where there is an unfavourable risk/benefit ratio; or (iii) take actions needed to reduce or eliminate hazards, but await clinical data before determining whether efficacy can be established.

Therapeutic Goods Order No. 80, *Child-resistant packaging requirements for medicines*, requires child-resistant packaging for oral medicines containing antihistamines, codeine, dihydrocodeine, phenylephrine or pseudoephedrine. Child-resistant packaging is not required for dextromethorphan, pholcodine, guaiphenesin or ipecacuanha, although significant numbers of ADRs have been reported to these substances in children in Australia and/or overseas.

The TGA paper made the following recommendations:

1. Safety, efficacy and availability: In light of the current lack of evidence of efficacy, as concluded in the [External Reviewers' Report], and the historical profile of ADRs in Australia and overseas, the risks associated with use of cough and cold medicines in children under 6 years of age are likely to outweigh the benefits. Therefore, it is recommended that labels of all OTC cough and cold medicines advise against use in

children under 6 years of age. The need for such warnings should be reviewed if robust efficacy data becomes available.

2. Packaging: Child-resistant closures were recommended for all OTC liquid cough and cold medicines, in the interests of consistency and improved safety.

Discussion

Members were advised that the minutes of the Panel's discussion and recommendations, together with the TGA's Internal Panel (final) Report and the [External Reviewers' Report] will be presented to the Medicines Evaluation Committee (MEC) on 30 July 2009. The MEC will be requested to provide advice and/or endorsement of the Panel's recommendations.

Stakeholder and public comment will then be sought on the Report and its attachments (minus any confidential information). Further advice may be sought from the MEC, prior to the TGA Delegate making a final decision. Members noted that, prior to preparation of the [External Reviewers' Report], industry was provided with the references and abstracts for papers that were sent to the external reviewers, and was asked to provide any further relevant information on the use of cough and cold medicines in children aged 2 years and over.

It was agreed that the minutes and conclusions of the TGA Internal Panel should be presented to the MEC with the TGA's Internal Panel Report (updated where appropriate) and its attachments.

The [External Reviewers' Report] and TGA paper concluded that there is no evidence for the efficacy of cough and cold products in children – this conclusion had also been reached by regulatory authorities in Canada, the UK and the USA.

Members noted that the [External Reviewers' Report] included a general review of safety of medication in children and childhood poisonings reported in New South Wales (on pages 11-14), but there was little information or discussion on ADRs due to cough and cold medicines. The table on page 8 of the TGA paper had therefore provided information on reports to the TGA between 1981 and May 2009 of ADRs in children for substances used in cough and cold medicines. While it was suggested that ADRs to cough and cold medicines seemed to be less frequent in Australia compared with the UK, USA and Canada, members noted that sales information would not provide useful information on their frequency, as ADR reporting for OTC medicines is not comprehensive.

Members queried whether the information on ADRs in the TGA paper included 'general listing' ADRs. It was agreed that this should be checked, and the information amended if appropriate².

A significant number of ADRs were reported in children 2 years and over, with a majority of those reported to the TGA occurring in children under 6 years. The Panel agreed with the contention in the TGA paper that the explanation for this is likely to be multifactorial, but may include the following:

- Inappropriate use: Assessment by parents or carers of symptoms in young children can be difficult. Younger children also have limited ability to communicate on their need for treatment or the effects of treatment.
- Inappropriate dosing: Dosing requirements of younger children may be weight, rather than age, dependent, while there is a large degree of overlap with population-based weight charts in this age group. Doses based on age that reflect population averages may be inappropriate for some children.

² Note: The finalised TGA Report includes an additional nine 'general listing' ADRs.

- Uncertainty regarding compliance: Lack of efficacy may be incorrectly assumed to be due to lack of compliance, leading to further dosing.
- An increased number of coughs and colds in this age group.

The TGA paper had concluded, based on a risk/benefit analysis, including these points and data on ADRs reported in Australia and overseas, that use of cough and cold medicines in children under 6 years of age is not appropriate.

Comments on pages 10-11 of the [External Reviewers' Report] indicated that parents may perceive sedation as being beneficial in helping a coughing child (and the parents) sleep and that, in some cases, use of OTC medicines to promote sleep may protect a child from physical abuse. Further review of the paper by Allotey et al³ was suggested, to determine whether it supports the review's contentions regarding 'social medication'⁴.

It was suggested that use of OTC cough and cold medicines is driven by factors including advertising to consumers, advice from medical practitioners or pharmacists, and simply by their availability. Members noted that advertising and education campaigns have successfully reduced expectations that antibiotics should be prescribed to patients with colds and flu, and suggested a similar approach to reduce use of OTC cough and cold medicines, on the basis that these products are not necessary, while their use in children is potentially harmful.

The [External Reviewers' Report] 'Summary and discussion' (pages 25-28) was noted. The review had recommended the following 'Possible courses of action' (pages 28-31):

- 15.1 – Maintain the 'status quo' (take no action; therefore, cough and cold medicines would continue to be available for use in children aged from 2 years);
- 15.2 – Take rigid action based strictly on evidence (exclude use of cough and cold medicines for children in age groups [eg. children under 6 years] where there is a lack of evidence of efficacy but there is a safety hazard, and the risks outweigh the benefits); or
- 15.3 – Take a more evolutionary approach (take actions needed to reduce or eliminate hazards, but await further clinical efficacy data in children, generated to current standards, before determining whether efficacy can be established).

In the last paragraph on page 62 regarding course of action 15.1, 'Maintain the status quo', the Panel disagreed with the statement "*This would be contrary to the usual decision-making process, where efficacy and safety are a prerequisite for approval of a new medicine. The fact that decision-making here involves re-evaluation of long-used drugs may not justify reversing the process.*", as it would be more appropriate to state "... *The fact that decision-making here involves re-evaluation of long-used drugs absolutely does not justify reversing the process*". Action 15.1 was considered inappropriate, since sponsors should be required to demonstrate efficacy of a product, rather than the TGA being required to demonstrate that it is not efficacious.

The Panel agreed that the available information indicates that there is evidence of risk with use of cough and cold medicines in children, and no evidence of efficacy (course of action 15.2). However, members suggested amendment of the wording to 'Take action based strictly on evidence', with deletion of the word 'rigid'. A cut-off of 6 years was considered appropriate as, while there did not appear to be evidence of substantial harm, the risks of using cough and cold medicines in children under 6 years of age appear to outweigh the benefits. The labels of paediatric cough and cold medicines should state that the products

³ Allotey P, Reidpath DD & Elisha D. 'Social medication' and the control of children: a qualitative study of over-the-counter medication among Australian children. *Pediatrics* 2004; 114: e378-e383

⁴ Note: The paper indicated that OTC cough and cold medications were used to achieve sleep, and not to prevent coughing.

should not be used for children under 6 years, and should not include dosage instructions for this age group.

With regard to recommendation 15.3 of the [External Reviewers' Report], the Panel asked that clinical efficacy, safety and pharmacokinetic data in children, generated to current standards, would be needed to support use in this age group.

The Panel also agreed that dosage instructions for paediatric OTC cough and cold medicines should state that these products should only be administered to children aged 6-12 years on the advice of a doctor or pharmacist. Members noted the MHRA's comment, that children aged 6 years and over can generally provide feedback to parents or carers on whether a medicine is making them feel better, whereas children younger than 6 years cannot generally provide this feedback. Together with the decreased risk of ADRs in children 6 years and older, this provided support for the Panel's proposal that use of OTC cough and cold medicines in children aged 6-12 years was acceptable on the advice of a doctor or pharmacist. However, use in younger children was not appropriate due to a poor risk/benefit profile.

It was suggested that the NDPSC could be requested to include substances used in cough and cold medicines in Schedule 3, when labelled for use in children aged 6-12 years, so all sales for this age group would require the intervention of a pharmacist. The NDPSC could also be requested to include these substances in Schedule 4, when used in cough and cold medicines for administration to children under 6 years of age.

The TGA paper had recommended that child-resistant closures should be required for all OTC liquid cough and cold medicines. The Panel supported this recommendation, but agreed further that child-resistant packaging should be required for all dose forms of OTC cough and cold medicines.

The Panel discussed whether its recommendations should apply to topical nasal decongestants containing oxymetazoline or xylometazoline. While there have been reports to the TGA of ADRs with oxymetazoline, including one serious ADR, the TGA paper did not indicate whether the serious ADR related to ingestion of a nasal spray. The Panel agreed that the full case reports for ADRs to oxymetazoline or xylometazoline could be reviewed, to determine whether products were used appropriately, and the intended route of administration. The TGA should also check whether any products containing oxymetazoline or xylometazoline for oral administration are marketed in Australia or overseas⁵. The Panel noted that the terms of reference for the [External Reviewers' Report] had included cough and cold medicines containing oxymetazoline and xylometazoline, and contended that industry could provide arguments or data to support the safety and efficacy of topical nasal decongestants in children, if it considers that the recommendations should not apply to those products.

The Panel agreed that topical nasal decongestants should be included in the TGA's review of the use of cough and cold medicines in children, as the TGA paper and [External Reviewers' Report] did not provide a justification for excluding those products. However, the MEC was requested to specifically consider whether the recommendations should apply to topical nasal decongestants for relief of symptoms of colds.

⁵ Note: Oxymetazoline and xylometazoline are available in Australia only as nasal drops, nasal spray and eye drops. There are no oral preparations available in Australia.

Summary and Recommendations

The Panel concurred with other regulators that had considered the use of OTC cough and cold medicine in children 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.

The Panel made the following recommendations in regard to OTC cough and cold medicines and their use in children;

- Labels of OTC paediatric cough and cold medicines should advise against use in children under 6 years, and should not include dosage instructions for this age group.
- Dosage instructions should state that paediatric OTC cough and cold medicines should only be administered to children aged 6-12 years on the advice of a doctor or pharmacist.
- Child-resistant packaging should be required for all OTC cough and cold medicines.
- Campaigns should be undertaken to educate 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 RACGP, ACRRM and the RACP, Pharmacy Guild, Consumers Health Forum and the pharmaceutical industry.
- The NDPSC could consider including substances used in cough and cold medicines in Schedule 3 when intended for administration to children aged 6-12 years, and in Schedule 4 for administration to children under 6 years of age.

The Panel agreed that the TGA paper should be amended and adopted to include the Panel's suggestions and recommendations.

The Panel also requested that the MEC provide comment and advice on the recommendations made by the Panel, and requested that the MEC specifically consider whether the recommendations should apply to topical nasal decongestants for relief of symptoms of colds.