Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

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In this issue

First-generation oral sedating antihistamines – use in children

Health professionals are reminded that first-generation oral sedating antihistamines, including promethazine oral liquid products, are not approved for use in children under two years of age due to the potential for fatal respiratory depression. You are also encouraged to educate parents and caregivers regarding this information.

The TGA recently reviewed this issue following a coronial hearing of a fatal case involving a 74-day old infant being given over-the-counter (OTC) promethazine oral liquid, a phenothiazine derivative that is a long-acting antihistamine with mild atropine-like anticholinergic effects and some anti-serotonin effects.

While the Coroner did not attribute the infant's death to ingestion of promethazine, they were concerned about the risk of respiratory depression when promethazine is given to infants and therefore recommended stronger Product Information (PI) and Consumer Medicine Information (CMI) warnings to advise prescribers, distributors, dispensers and consumers that promethazine is contraindicated in infants under two years of age.

The TGA's investigation found that most promethazine oral liquid products do have warnings on their labels advising against use in children under two years, as per the Australian Regulatory Guidelines for OTC Medicines (OTC guidelines) Appendix 5. Other international regulatory agencies, such as the US Food and Drug Administration, Health Canada, the European Medicines Agency and New Zealand's Medsafe, also contraindicate the use of promethazine in children under two years of age.

The risk of respiratory depression in infants also applies to other first-generation oral sedating antihistamines.

OTC products containing first-generation sedating antihistamines include:

- promethazine
- brompheniramine
- chlorpheniramine
- dexchlorpheniramine
- diphenhydramine
- doxylamine
- pheniramine
- alimemazine (trimeprazine)
- triprolidine.

Adverse events

To 15 November 2017, the TGA database of adverse event notifications contains 45 reports of adverse events in children aged under two years in which a first-generation oral sedating anti-histamine is listed as the sole-suspected medicine. These reports document a range of adverse events including hypersensitivity reactions, agitation, abnormal movements, vomiting and diarrhoea.

The NSW Poisons Information Centre has provided the TGA with evidence of ongoing intentional use of promethazine oral liquid products in children under two years of age. There have been international reports of fatal respiratory depression in children under two who have been given promethazine, and

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TGA Health Safety Regulation

therefore we are reminding health professionals that these products should not be prescribed or recommended for children under two years of age.

Regulatory response

In response to this safety concern, the TGA will be seeking to make the statement 'Do not give to children under two years of age' (which is currently a recommended statement in the applicable OTC guidelines) a mandatory warning statement on the labels of OTC liquid oral formulations of first-generation oral sedating antihistamines.

The TGA will also work with sponsors to strengthen these warnings in the PI and CMI documents for these products where applicable.

In the meantime, health professionals are encouraged to discuss this issue with parents and caregivers, and to report any adverse events involving first-generation oral sedating antihistamines to the TGA.

Suvorexant (Belsomra) – next day effects

Health professionals are advised to discuss potential adverse events, especially next day residual effects, with patients before prescribing suvorexant.

Suvorexant is a highly selective reversible high affinity orexin receptor antagonist. It is indicated for the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance, and is marketed in Australia under the brand name Belsomra.

Belsomra was entered on the Australian Register of Therapeutic Goods on 16 November 2016. It is not listed on the Pharmaceutical Benefits Scheme.

Since registration, the TGA has received a number of reports of adverse events, including sleep paralysis, gait disturbance, hallucination, headache and paraesthesia.

These potential side effects, including next day residual effects, are well communicated in the Product Information, but it is important for patients to be warned of these potential adverse events before they are prescribed suvorexant.

The Consumer Medicine Information (CMI) document for Belsomra advises patients to 'Be careful driving, operating machinery or other activities that require complete alertness until you know how Belsomra affects you. As with other medicines used to treat insomnia, Belsomra may cause drowsiness in some people the day after taking it. Do not drive or do other dangerous activities until you feel fully awake.'

The CMI also advises that 'After taking Belsomra, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing, such as sleep walking, eating, talking or driving a car. The next morning, you may not remember that you did anything during the night.' If this occurs, the patient or their carer/family should inform the doctor immediately.

You are encouraged to remind patients that this medication should not be taken if they drink alcohol that evening or before going to bed, or if they have taken other medicines that make them sleepy, as it may increase the risk of these adverse events occurring.

In addition to discussing these potential adverse events with your patient, and potentially any caregivers or immediate family members, consider providing them the CMI.

Please report any suspected adverse event associated with Belsomra. This will assist the TGA to monitor the safety of this product.

Desvenlafaxine (Pristiq) recommended dose

Health professionals are reminded that the recommended dose of desvenlafaxine (Pristiq and generic versions) is 50 mg once daily and that the maximum dose should not exceed 200 mg/day.

The Product Information for Pristiq has recently been updated to include the following:

Initial Treatment

The recommended dose for Pristiq is 50 mg once daily, with or without food. In clinical trials, no additional benefit was demonstrated at doses greater than 50 mg/day. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur gradually and at intervals of not less than seven days. The maximum dose should not exceed 200 mg/day.

Prescribing above this dose may increase the risk of patients experiencing adverse events.

Miconazole and potential interaction with warfarin

Health professionals are reminded that, while the number of Australian reports is low, the potential interaction between miconazole and warfarin can be life-threatening.

Miconazole is an antifungal medication used to treat ringworm, pityriasis versicolor, and yeast infections of the skin or vagina.

Products affected by this issue are miconazole preparations for topical oral mucosal use and topical vaginal use. There are three such products included on the Australian Register of Therapeutic Goods:

- Daktarin Oral Gel
- Decozol Oral Gel
- Resolve Thrush Cream.

The potential for an interaction between miconazole and warfarin is well-documented. The TGA has previously published information about this safety issue in 1998 and 2002.

Miconazole inhibits one of the main cytochrome P450 isoenzymes involved in warfarin metabolism (CYP2C9), which can result in reduced warfarin clearance and an enhanced anticoagulant effect. This can lead to supra-therapeutic international normalised ration (INR) values and subsequent bleeding complications. Bleeding events can have fatal outcomes.

The TGA will be seeking to make the statement 'Ask your doctor or pharmacist before use if you are taking warfarin, a medicine used to thin the blood, because bleeding or bruising may occur' (which is currently a recommended statement in the OTC guidelines for topical antifungal medicines) a mandatory warning statement on these products.

The TGA will also work with sponsors to strengthen the warnings in the PI and CMI documents for these products. In the meantime, health professionals are encouraged to discuss this issue with patients, and to report any adverse events involving miconazole.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines (see Black Triangle Scheme)
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **online** at www.tga.gov.au
- **by email** to ADR.Reports@tga.gov.au
- **by fax** to 02 6232 8392
- **using the 'blue card'** available from the TGA website

For more information about reporting, visit www.tga.gov.au or contact the TGA's Pharmacovigilance and Special Access Branch on 1800 044 114.

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